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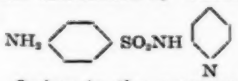
BONE MARROW CHANGES IN ACUTE INFECTIONS AND THE EFFECTS OF SULPHONAMIDES ON THE MARROW.[1]

By T. E. WILSON, M.D., B.S., B.Sc. (Melbourne), M.R.A.C.P.,

The Prince Henry Hospital, Sydney.

THE sulphonamides, although known to the chemists for decades, have within the past few years rapidly become one of the most important groups of synthetic compounds used in chemotherapy. The sulphonamide group SO_2NH_2 seems to be therapeutically active in pneumococcal and other infections only when attached to the benzene ring. The most important sulphonamide derivative, because of its wide field of effectiveness and its low toxicity, is sulphapyridine, "Dagenan" or "M & B 693". This was introduced by Whitby[(1)] in 1938, and has the formula



(Buttle[(2)]).

Owing to the presence of the benzene ring in sulphapyridine and related compounds, it might readily have been suggested by analogy with other benzene derivatives that the toxic action of these drugs would include depression of the bone marrow, and it is with this effect that this paper is concerned.

REVIEW OF THE LITERATURE.

In the past four years more than 50 cases of neutropenia and agranulocytosis, 30 cases of hæmolytic anæmia and one case of leucoerythroblastic anæmia[(7)] have been reported associated with sulphonamide therapy. These include the report of Spain[(35)] of a patient suffering from mastitis who was treated with nine grammes of sulphapyridine and "Proseptasine" over a period of five days, and who developed fatal agranulocytosis. This is the smallest amount of the drugs administered which was followed by fatal agranulocytosis. Kohn[(20)] described a case of *otitis media* in a baby who developed acute hæmolytic anæmia after the administration of 2·4 grammes of sulphanilamide in four days. Fortunately, the child recovered. In the majority of the reported cases, however, much larger doses over longer periods were used. Sulphanilamide was the drug used for all patients who developed hæmolytic anæmia, with the exception of one patient reported by Antopol *et alii*,[(31)] to whom "Prontosil" was given; and to date no case of hæmolytic anæmia has been reported to follow the use of sulphapyridine. In no case was the administration of "Uleron" associated with the development of neutropenia. This is surprising when one considers the frequency with which other toxic phenomena occur during the use of "Uleron", and would be a very weak argument in favour of the use of "Uleron" instead of sulphapyridine.

In some of the reported cases the sulphonamides were given by injection, in others orally; and there appears to be no relationship between the mode of administration and the development of toxic symptoms.

Working with rats, Machella and Higgins[(22)] were able to show that sulphanilamide regularly produced an anæmia, the degree of which was dependent on the dose used and on the duration of the administration, and from which recovery could occur on cessation of the drug.

There has been some discussion, however, concerning the frequency with which neutropenia in man follows sulphonamide therapy. Agranat *et alii*[(37)] report slight and transient changes in the peripheral blood following sulpha-

[1] Part of this investigation was carried out during the tenure of a Junior Fellowship in Surgery at the Prince Henry Hospital, Sydney.

pyridine therapy. Lloyd *et alii*,[34] Britton and Howkins[28] and Bigler *et alii*[35] noted a slight but definite neutropenia in many cases when sulphonamides were given; but Evans and Gaisford[37] and Anderson and Dowdeswell[38] deny that this occurs. Methæmoglobin is quite a common finding after the administration of the sulphonamides (*vide* Bensley[39]), but does not seem to be directly related to the production of hæmolytic anæmia. Campbell[40] reports that sulphanilamide may stimulate a slight reticulocytosis without a necessarily associated anæmia or leucopenia. Myhre[41] observed basophilic stippling of the erythrocytes and slight anæmia following sulphanilamide therapy; but in his cases large doses of the drug were used.

So far, no case of purpura or of aplastic anæmia associated with the use of the sulphonamides has been reported. This is of interest, for in view of the presence of the benzene ring in the sulphonamides used therapeutically, it might have been postulated that these blood dyscrasias would develop after sulphonamide medication.

The resemblance of the cases of acute hæmolytic anæmia associated with sulphonamide therapy to the idiopathic cases is very close; and one wonders how many of these patients first developed the acute hæmolytic anæmia and then had sulphonamides given to them because of the fever and leucocytosis.

Strangely enough, in only 13 of the reported cases of depression of the bone marrow complicating the use of the sulphonamides was the marrow examined and then, for the most part, only incompletely. Nicol and Freedman[22] found no leucopoiesis and only mild erythropoiesis in the sternal marrow; Bresgen[13] found no neutrophile cells, Pearson[20] found many mononuclear cells but no polymorphonuclear cells, and Robb[23] found few granular cells. Myhre[37] reports that sternal puncture, when the peripheral blood contained 3,000 white cells per cubic millimetre and 1% staff forms, revealed no alteration of the erythropoietic system except basophilic stippling as in the blood, no increase of reticulum cells, megakaryocytes, lymphocytes, plasma cells or monocytes, absolutely no granulocytes with segmented nucleus or staff nucleus, but the ordinary number of myelocytes, promyelocytes and myeloblasts, and more mitoses than normal. Four days later, after treatment with "Campolon", the white count had returned to normal, and after a further fortnight sternal puncture revealed a preponderance of the granulopoietic system with excess of the mature forms, staffs or segments. In this case lead poisoning, as a cause for the stippling, was excluded.

Young[15] reports a complete absence of all granular cells, both neutrophile and eosinophile, while cells of the lymphocytic series, megakaryocytes and nucleated red cells were numerous in the red marrow.

Garvin[21] in his first case reported the post-mortem findings of maturation arrest of the myeloid series with stem cell hyperplasia and the absence of more mature cells. In this case an absolute agranulocytosis was present just before death. In his second case, in which the number of white cells in the peripheral blood fell to 1,350 per cubic millimetre, 20% being neutrophile cells, examination of the marrow revealed a distinct shift to the left in the myeloid series, with a reversion to the stem cell type. There were occasional myeloid cells with granules and a small number of polymorphonuclear cells. There was a distinct increase in the reticulum cells, while the red cell series showed no significant change.

Dolgopol and Hobart[20] aspirated sternal marrow from their patient suffering from agranulocytosis three days before death, and they also examined the marrow *post mortem*. The biopsy revealed that 1·5% were primitive cells, 5·5% were myeloblasts, 2·5% were promyelocytes, 0·5% were basophile myelocytes, 1% were plasma cells, 89% were lymphocytes, and nucleated erythrocytes numbered four to every 100 white blood cells. The post-mortem specimens showed a slight decrease in number of the nucleated cellular elements in some areas, but the marrow was not depleted as a whole. A small number of granular myelocytes and one or two polymorphonuclear cells were seen. The reticulum cells were prominent. Many normoblasts were scattered throughout the sections, but they were not arranged in erythroblastic foci. The megakaryocytes were quite numerous and many lymphocytes were present. The sinuses were distended and contained many red blood cells and rare mononuclear cells.

Schwartz, Garvin and Koletsky[16] found at autopsy in their case in which the leucocytes fell to 800 per cubic millimetre, that the cellularity of the hæmopoietic tissues was within normal limits, and that the differential count on the marrow smears revealed 55% myeloblasts, 35% lymphocytes, 15% nucleated red blood cells (I am quoting their figures from *The Journal of the American Medical Association*) and an occasional plasma cell. They define the myeloblast as a large stem cell with a vesicular nucleus, the chromatin of which was arranged in fine strands; the nucleoli were prominent and the cytoplasm stained a homogeneous pale blue and showed no granule formation. They alone mention that no degenerative changes were present in the myeloid cells. Their sections showed a complete absence of adult polymorphonuclear cells and even of myelocytes. Most of the red cells were late normoblasts, with a few erythroblasts and a moderate number of degenerative forms. Megakaryocytes were present in all preparations, and there were many large phagocytic cells containing iron pigment. They concluded that the sulphanilamide in their case exerted a toxic effect on both the red and white blood cells series.

Sheckett and Price[32] report the following results for a sternal biopsy count: polymorphonuclear cells, 0·2%; eosinophile cells, 1%; eosinophile myelocytes, 1%; basophile cells, 1%; blasts, 1%; lymphocytes, 49%; normoblasts, 43%; and megaloblasts, 4%. At the post-mortem examination on this patient (aged forty-five years) there were no cellular elements in the marrow at the upper end of the femur and moderately cellular marrow at the upper end of the humerus; a differential count gave the following results: primitive cells, 4%; blast forms, 40%; myelocytes, 6%; lymphocytes and plasma cells, 30%; megaloblasts, 5%; and normoblasts, 15%.

Rosenthal and Vogel[26] report the marrow findings in two cases of neutropenia associated with sulphapyridine therapy. In the first case the patient was a boy, aged twelve months, suffering from pneumonia; the number of white cells fell to 1,100 per cubic millimetre, 8% being neutrophile cells, and examination of aspirated sternal marrow revealed 60,000 nucleated cells and 88 megakaryocytes per cubic millimetre, 1·4% myeloblasts, 71% myelocytes, many of which contained "toxic" granules, 1·8% eosinophilic myelocytes, 1·2% non-segmented neutrophile cells, 1·4% segmented neutrophile cells, 2·4% eosinophile cells, 0·2% basophile cells, 3·2% lymphocytes, 1·6% hæmatogones, 0·2% reticulum cells, 3·6% erythroblasts, 1·8% normoblasts and 0·2% megakaryocytes. After blood transfusions and liver extract injections, the child recovered. Their second patient, a boy, aged ten years, suffering from acute osteomyelitis of the right humerus, after treatment with sulphapyridine developed a neutropenia of 3,400 white cells per cubic millimetre; but despite treatment by blood transfusion and "Pentnucleotide" the white cells decreased to 300 per cubic millimetre. At this stage examination of aspirated sternal marrow revealed that the total number of nucleated cells was 25,000 per cubic millimetre, 3·5% myelocytes, 0·5% segmented neutrophile cells, 32% lymphocytes, 3·5% hæmatogones, 1% plasma cells, 2% reticulum cells, 1·5% erythroblasts and 56% normoblasts. Death occurred two days after the sternal biopsy.

In only two of the cases of acute hæmolytic anæmia associated with sulphonamide therapy have the bone marrow findings been reported. In Wood's case[40] the sections from the sternum and lumbar vertebræ showed hyperplastic hæmatopoietic tissue, and those from the proximal portion of the right femur showed a few small foci of hæmatopoietic tissue. Sections from the distal end of the right femur and the proximal end of the right tibia were entirely fatty, with no foci of hæmopoietic tissue. The sections from the lumbar vertebræ contained basophile erythroblasts 1·7%, polychromatophile erythroblasts 37·8%, normoblasts 7·3%, erythrocytes 13·1%, heterophile promyelocytes 0·7%, heterophile myelocytes 11·1%, hetero-

phile metamyelocytes 11·8%, heterophile leucocytes 4·0%, eosinophile cells 4·0%, megakaryocytes 1·3% and unidentified cells 12·6%.

In Koletsky's case[29] the cellularity of the marrow was within normal limits. The differential count showed that 17% were erythroblasts, 25% were normoblasts, 46% were myeloid cells (chiefly myelocytic and metamyelocytic forms), and 12% were stem cells. The usual number of megakaryocytes was present.

In all of these cases of neutropenia in which the marrow was examined, it appeared that associated with the neutropenia of the peripheral blood there was a partial or a complete disappearance of the adult granular cells from the marrow, together with an increase in the more primitive cells of the granular series. A slight hyperplasia of the nucleated red cells of the marrow is described in the two cases of acute hæmolytic anæmia in which the marrow was examined. Some degenerative changes in the nucleated red cells of the marrow were found in one case of hæmolytic anæmia; but no other abnormality in the cytology of the marrow cells has been found in these cases. It is of interest to note that the platelets did not appear to be affected by the administration of the sulphonamides. So far, only one case has been reported in which the number of platelets was decreased, that of Rosenthal and Vogel,[28] and in this case the number of 160,000 platelets per cubic millimetre was a slight decrease from normal and probably represents only a depression of the marrow by the acute pyogenic infection. Also, no cases have been reported of purpura or aplastic anæmia associated with sulphonamide therapy.

Some writers, for instance Sheckett and Price,[25] think that the quantity and the prolonged use of the drugs are significant factors in the production of depression of the marrow, and they do not agree that the action on the marrow is the result of a specific idiosyncrasy. From an examination of the above case reports it is not possible to be sure of the absence or presence of a specific idiosyncrasy; and although slight but definite reductions in the number of the circulating white cells frequently occur during or after treatment with the sulphonamides (Britton and Howkins,[55] and Bigler *et alii*[56]), when one considers the relatively few people who develop signs of depression of the marrow during treatment with sulphonamides, it appears likely that in these cases there is some other factor at work in addition to the drugs, be it a specific idiosyncrasy or be it the combined action of the infection and the drug on the marrow. Osgood[62] studied the action of sulphanilamide on the *in vitro* cultures of human marrow, and showed that in concentrations less than one in 1,000 there was no evidence that the marrow cells were damaged by the sulphanilamide. When the cases of agranulocytosis and of acute hæmolytic anæmia associated with sulphonamide therapy were reviewed, it was found that in no instance did the blood sulphonamide level exceed 0·01%. In one of the cases of agranulocytosis (Borst[40]) there was a previous history suggestive of *purpura hæmorrhagica* with spontaneous recovery, and thus perhaps an underlying abnormality of the marrow was present at the time of the administration of the sulphonamide. In all the reported cases of acute hæmolytic anæmia, pyrexia and a pronounced leucocytosis (up to 87,000 per cubic millimetre in Harvey and Janeway's patient[27]) have been present. In two of the cases[27][38] the Wassermann test produced a reaction. When these facts are considered, the resemblance of these cases to other cases of hæmolytic anæmia not associated with sulphonamide therapy will be seen.

Kohn[38] was able to reproduce toxic symptoms with small doses of sulphanilamide two weeks after his patient had recovered from acute hæmolytic anæmia. McGuire and McGuire,[19] two months after their patient had recovered from agranulocytosis, were again able to produce a rapid decline in the number of white cells by the exhibition of sulphanilamide. Wood[30] was able to produce with sulphanilamide a second rapid fall in hæmoglobin level in his case of hæmolytic anæmia.

Harvey and Janeway,[27] on repeating the administration of sulphanilamide in their two cases of hæmolytic anæmia, were unable to reproduce the previous symptoms, and Long and Bliss[45] were unable to produce a second attack of neutropenia in their case.

Following the suggestions of Colebrook and Storer,[63] Johnston[14] successfully used heparinized blood for transfusion in his cases of agranulocytosis. If, as Colebrook and Storer report, the leucocytes are damaged by citration of the blood but not by heparinization, it certainly appears correct to adopt this latter method when giving blood transfusions to patients with agranulocytosis or neutropenia.

OBSERVATIONS.

I have examined the marrow from 20 patients treated with sulphonamides in various amounts and for different periods, either during treatment or immediately after

TABLE IA.
Patients not Treated with Sulphonamides.

Diagnosis.	Age in Years.	Marrow Findings.																Blood Findings.[1]	
		Polymorphonuclear Cells. (Percentage).	Metamyelocytes. (Percentage.)	Myelocytes. (Percentage.)	Premyelocytes. (Percentage.)	Myeloblasts. (Percentage.)	Eosinophile Cells. (Percentage.)	Basophile Cells. (Percentage.)	Monocytes. (Percentage.)	Lymphocytes. (Percentage.)	Plasma Cells. (Percentage.)	Normoblasts. (Percentage.)	Erythroblasts. (Percentage.)	Megaloblasts. (Percentage.)	Histiocytes. (Percentage.)	Mitotic Figures. (Percentage.)	Ratio of Red to White Cells.	Megakaryocytes.	Hæmoglobin Percentage.	White Cells per Cubic Millimetre.
Acute appendicitis ..	68	1·2	27·6	40·4	0·4	—	2·4	—	—	9·2	—	16·8	2·0	—	—	—	1 : 4·3	—	74	22,400
Hepatic abscess ..	49	14·5	17·4	29·3	2·1	—	2·4	0·1	—	10·1	—	24·1	—	—	—	—	1 : 3·2	0·1	69	10,400
Mediastinal abscess ..	58	21·2	29·6	21·2	0·2	—	7·0	—	0·4	10·4	0·6	9·4	—	—	—	—	1 : 9·6	—	92	18,400
Pericarditis ..	1	—	4·0	40·1	—	—	3·2	—	—	2·4	—	46·2	2·5	—	1·6	—	1 : 1·1	—	45	21,400
Meningitis ..	12	9·4	13·2	8·2	—	—	4·4	—	0·6	6·0	—	58·0	0·2	—	—	—	1 : 0·72	—	90	12,500
Cerebral abscess	6	5·0	14·2	5·4	0·8	0·8	1·6	0·2	—	6·4	0·4	63·2	1·6	—	0·4	—	1 : 0·54	0·1	78	6,200
Acute lymphadenitis	4	21·4	13·8	18·2	2·1	0·2	1·4	—	0·6	2·2	—	39·5	0·6	—	—	—	1 : 1·5	0·2	65	26,200
Bronchopneumonia	42	6·4	33·6	37·0	0·8	—	5·4	—	—	4·0	2·0	9·8	—	—	1·0	—	1 : 9·2	—	87	8,400
Meningitis ..	7	15·2	34·6	10·6	—	—	4·4	—	—	4·4	—	29·4	1·2	—	0·2	—	1 : 2·3	—	92	13,400
Meningitis ..	9	9·4	23·4	11·0	0·2	—	1·6	—	—	1·4	—	52·2	0·4	—	—	0·4	1 : 0·90	—	56	15,000
Peritonitis ..	64	11·2	32·4	6·5	0·1	—	—	—	0·1	10·2	0·5	32·5	4·0	0·9	1·3	0·3	1 : 1·6	0·1	84	18,500
Appendiceal abscess	52	6·6	42·3	22·1	0·4	—	4·0	—	—	12·1	0·4	8·0	3·3	0·1	0·1	0·6	1 : 7·8	0·1	72	17,500
Bronchopneumonia	65	2·2	15·5	14·9	—	0·2	2·3	—	0·6	4·3	1·9	48·7	8·1	1·0	—	0·3	1 : 0·73	0·1	78	18,300
Ischio-rectal abscess	69	2·0	7·4	13·0	0·6	0·4	4·0	0·2	0·3	2·8	0·4	63·9	3·9	0·2	0·7	0·2	1 : 0·47	—	82	14,500
Septicæmia ..	41	35·8	15·9	6·0	0·7	0·2	2·4	0·2	0·1	14·4	0·7	20·1	3·2	0·3	—	—	1 : 3·2	0·1	67	23,500
Peritonitis ..	65	4·7	14·6	24·4	2·8	1·9	2·7	—	0·1	9·7	2·4	29·3	4·8	1·6	0·5	0·5	1 : 1·8	—	84	14,600
Peritonitis ..	55	3·6	45·0	8·0	—	—	4·2	0·4	—	5·8	0·2	32·4	0·4	—	—	—	1 : 2·0	—	59	17,800
Cellulitis ..	47	5·4	57·6	8·5	0·4	—	2·8	—	—	5·3	0·2	15·9	3·8	—	—	0·1	1 : 4·1	0·1	84	18,500
Lobar pneumonia	57	14·0	44·0	11·6	0·4	0·2	2·2	—	0·1	4·1	0·4	22·0	0·9	—	—	0·1	1 : 3·4	0·1	64	25,400
Ulcerative colitis ..	49	7·1	39·6	3·4	0·1	0·1	1·3	—	—	7·0	0·7	37·9	2·4	—	—	0·4	1 : 1·5	0·1	42	14,900

[1] The blood findings given in Tables IA and IB were those obtained either at the time of the marrow biopsy or immediately before death.

death, and in no case was I able to find changes in the marrow cells, either quantitatively or qualitatively, which were not present in the marrow from a similar series of patients who had not had treatment with sulphonamides.

Methods.

The methods of preparation of the specimens and the nomenclature used have been discussed in a previous article.[66] To obtain the biopsy specimens sternal punctures were performed, as I did not feel justified in trephining patients who were not going to benefit by the operation. Except in Case I, Table Ib, the examination of the marrow in these cases was confined to smears from emulsified curettings or from aspirated material.

Report of a Case and Marrow Findings.

The marrow was examined from 20 patients suffering from infection treated with sulphonamides and from 20 similar patients without such treatment. This second series was collected before the entry of the sulphonamides into clinical medicine, and in the present era of sulphonamide medication in practically all cases of infection, this latter series must rapidly become a pathological rarity.

Owing to the many reports of successful treatment of pneumococcal meningitis with "Prontosil" by Caldwell and Byrne,[65] with sulphanilamide by Young,[66] and with sulphapyridine by Reid and Dyke,[67] Robertson,[68] Cutts *et alii*,[69] Cable,[70] Terry and Beard[71] and Falla,[72] Case I, Table Ib, is of interest; although the patient was given 159 grammes of sulphapyridine over a period of forty-two days, at no time did the pneumococci disappear from the cerebro-spinal fluid. Experimentally, the development of a tolerance by the pneumococci for sulphapyridine has been demonstrated by Maclean *et alii*,[73] among others, and it appears that in this case a definite tolerance developed.

B.H., aged three years, was admitted to the Children's Hospital, Melbourne, in the care of Dr. J. W. Grieve and Dr. Boyd Graham, complaining of earache of three days' duration and of drowsiness and vomiting of one day's duration. On examination he appeared to be listless and flushed; pronounced neck stiffness and some head retraction were present and Kernig's sign was elicited; both tympanic membranes were red, but not bulging. The cerebro-spinal fluid was turbid and under normal pressure, and contained 4,000 cells per cubic millimetre, mostly polymorphonuclear, and Type XIV pneumococci. A blood count revealed that the leucocytes numbered 9,800 per cubic millimetre and the hæmoglobin value was 80%. The child's temperature on his admission to hospital was 104·6° F.

Treatment was immediately started with one gramme of sulphapyridine every four hours for three doses, and then 0·5 gramme every four hours. After one week the dose was reduced to 0·25 gramme every four hours; but this was immediately followed by a recrudescence of the former signs and symptoms which had practically disappeared. Moreover, the number of cells in the cerebro-spinal fluid, which had decreased to 36 lymphocytes per cubic millimetre, began to rise again. Although the number of cells had fallen so much, culture from the cerebro-spinal fluid continued to yield pneumococci, and at no time were attempts at culture unsuccessful. Despite blood transfusions, the continued administration of sulphapyridine, both orally and parenterally, and repeated lumbar and cisternal punctures, death occurred six weeks after the child's admission to hospital. During these six weeks the temperature swung from 99° to 105° F., the number of white blood cells varied from 10,000 to 15,000 per cubic millimetre, and the total blood sulphonamide content varied from 12·5 to 18·0 milligrammes per 100 cubic centimetres. Three days before death the blood findings were as follows: hæmoglobin value, 51% (7·1 grammes); red blood cells, 3,010,000 per cubic millimetre; colour index, 0·85; white blood cells, 13,600 per cubic millimetre, 13·5% being neutrophile polymorphonuclear cells, 19% old metamyelocytes, 1% eosinophile cells, 17% monocytes and 49·5% lymphocytes. The erythrocytes were well hæmoglobinized and many polychromatophile cells were present. Many platelets were seen and many of the neutrophile cells contained "toxic" granules. The differential leucocyte count thus revealed a shift to the left in the granular series, relative neutropenia and an absolute lymphocytosis and monocytosis. Bone marrow was obtained from the sternum within a few minutes of death. Smears were prepared from curettings emulsified in serum which had been collected from the patient during life, and sections were made from material fixed and decalcified in Zenker's solution with acetic acid.

At autopsy there was a thick, yellow, fibrinopurulent exudate over the entire cortex; but apart from engorgement and cellular infiltration no abscess formation was observed in the brain substance. Both middle ear cavities appeared normal. There was a slight degree of congestion in the bases of both lungs, but no other pathological process was found in the lungs. A hydroureter and hydronephrosis were present on the left side, but otherwise the renal tracts appeared normal. The gastro-intestinal and cardio-vascular systems appeared to be normal.

The marrow smears were found to be very cellular and a differential count gave the following figures: eosinophile cells 6·5%, basophile cells 0·5%, old metamyelocytes 2·4%, young metamyelocytes 4·0%, myelocytes 17·1%, premyelocytes 0·2%, myeloblasts 0·6%, monocytes 2·1%, lymphocytes

Table Ib.
Patients Treated with Sulphonamides.

Diagnosis.	Age in Years.	Amount of Drug Given. (Grammes.)	Duration of Treatment. (Days.)	Marrow Findings.																Blood Findings.[1]	
				Polymorphonuclear Cells. (Percentage.)	Metamyelocytes. (Percentage.)	Myelocytes. (Percentage.)	Premyelocytes. (Percentage.)	Myeloblasts. (Percentage.)	Eosinophile Cells. (Percentage.)	Basophile Cells. (Percentage.)	Monocytes. (Percentage.)	Lymphocytes. (Percentage.)	Plasma Cells. (Percentage.)	Normoblasts. (Percentage.)	Erythroblasts. (Percentage.)	Megaloblasts. (Percentage.)	Histiocytes. (Percentage.)	Mitotic Figures. (Percentage.)	Ratio of Red to White Cells.	Megakaryocytes.	Hæmoglobin Percentage.	White Cells per Cubic Millimetre.
Pneumococcal meningitis	3	159·0	42	—	6·4	17·1	0·2	0·6	6·5	0·5	2·1	16·9	0·3	48·4	1·0	—	—	—	1 : 1·0	0·2	51	13,600
Frontal abscess	4	16·0	5	1·2	7·6	5·6	0·2	—	3·2	—	0·2	2·0	—	80·0	—	—	—	—	1 : 0·25	—	54	12,800
Empyema thoracis	1	48·0	27	0·2	8·0	60·0	1·6	—	6·4	—	—	3·4	—	20·4	—	—	—	—	1 : 3·9	0·2	63	34,500
Empyema thoracis	10	5·0	1	2·2	70·8	7·8	—	—	3·2	—	—	1·6	—	14·0	0·4	—	—	—	1 : 5·9	—	56	43,400
Otitis media	2	4·0	1	0·8	13·8	44·8	0·4	—	3·6	—	0·2	3·0	—	32·2	1·2	—	—	—	1 : 2·0	—	84	17,500
Empyema thoracis	1	8·0	2	2·4	54·0	17·0	0·8	0·1	1·5	—	0·2	3·1	—	18·2	2·2	—	0·2	0·3	1 : 3·9	0·2	36	20,000
Bronchopneumonia	11	8·0	2	1·8	36·8	7·0	—	—	10·3	—	—	3·4	1·1	36·7	2·9	—	—	—	1 : 1·5	—	87	6,500
Carbuncle	2	39·0	13	2·4	12·7	51·0	0·2	—	0·8	0·4	0·3	5·2	0·8	23·4	0·6	—	1·2	1·0	1 : 3·1	—	44	24,500
Empyema thoracis	3	63·0	21	1·0	18·2	11·1	1·2	1·3	6·0	—	0·4	4·2	3·1	52·5	1·0	—	—	—	1 : 0·87	—	72	17,300
Septicæmia	65	16·0	2	2·4	15·2	45·4	2·8	0·4	1·8	—	0·2	8·2	0·4	5·6	16·2	—	0·6	0·8	1 : 3·6	—	84	18,300
Streptococcal meningitis	17	40·0	5	18·0	52·0	6·0	0·6	—	4·0	—	0·3	1·7	2·3	11·0	3·4	—	0·3	0·4	1 : 5·9	0·3	78	10,600
Acute gastro-enteritis	8	8·0	2	0·2	4·2	4·8	0·8	—	1·2	—	0·2	1·8	—	84·2	2·6	—	—	—	1 : 0·13	0·2	32	24,500
Hepatic abscess	32	6·0	1	22·4	45·0	9·4	—	—	—	—	—	6·0	—	17·2	—	—	—	—	1 : 4·8	—	77	6,700
Acute osteomyelitis	12	9·0	3	0·2	9·8	10·2	—	—	0·2	—	—	1·4	—	76·6	1·6	—	—	—	1 : 0·28	—	82	30,000
Scarlet fever	1	3·0	1	10·5	25·4	25·3	0·9	0·1	2·4	0·4	—	6·0	—	29·0	—	—	—	—	1 : 2·4	0·1	70	10,800
Streptococcal meningitis	1	21·0	14	4·2	12·0	10·2	—	—	0·4	—	—	0·4	—	72·6	—	—	—	0·2	1 : 0·38	—	54	41,200
Cellulitis	36	58·0	15	16·3	23·6	12·2	1·2	0·9	1·2	0·6	0·2	6·7	0·6	28·3	6·4	1·3	—	0·5	1 : 1·8	0·1	73	20,500
Bronchopneumonia	13	13·5	3	0·4	4·6	3·6	—	—	—	—	—	0·2	1·6	87·2	2·4	—	—	—	1 : 0·12	—	82	40,000
Empyema thoracis	12	42·3	14	1·6	37·0	32·4	0·4	—	0·4	—	—	1·6	—	25·2	1·4	—	—	—	1 : 2·8	—	90	26,000
Cellulitis	47	32·0	4	9·8	70·4	5·4	—	—	1·4	—	—	10·0	0·8	2·0	0·2	—	—	—	1 : 44·5	—	72	35,400

[1] The blood findings given in Tables Ia and Ib were those obtained either at the time of the marrow biopsy or immediately before death.

ILLUSTRATIONS TO THE ARTICLE BY DR. T. E. WILSON.

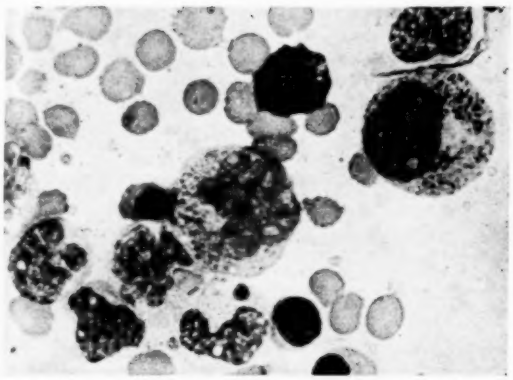


FIGURE I.
Smear of sternal marrow from B.H., aged three years (pneumococcal meningitis), showing two early myelocytes with "toxic" granules; one of these cells contains an irregular nucleus.

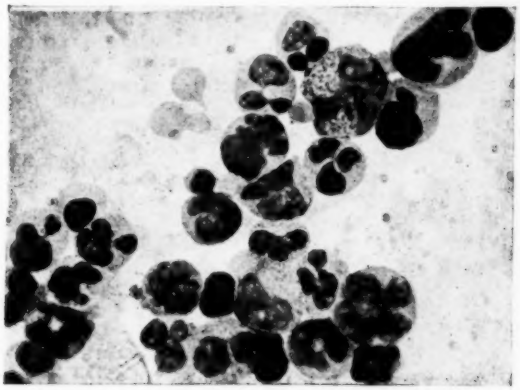


FIGURE II.
Smear of sternal marrow from M.D., aged two years (cellulitis of the face), showing budding and partial nuclear division of the nuclei of developing granular cells. A few of these cells show "toxic" granules in the cytoplasm.

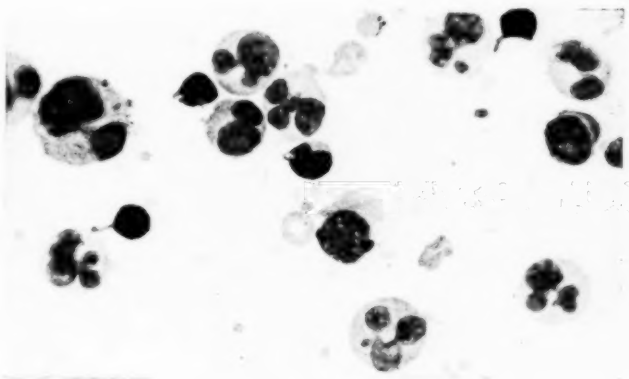


FIGURE III.
Smear of sternal marrow from J.F., aged seven years (meningitis), showing nuclear budding and partial nuclear division of the meta-myelocytes and of one myelocyte.

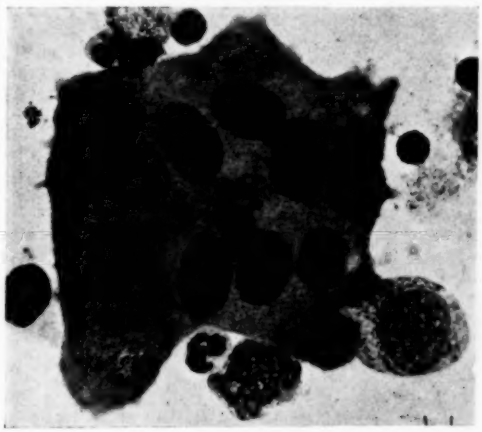


FIGURE IV.
Smear of marrow from M.P., aged ten years, showing a large multinucleated giant cell or polykaryocyte, probably an osteoclast. Some indication of the size of this cell may be gained by comparison with the myelocyte in contact with it.

FIGURE V.
Smear of sternal marrow from M.F., aged two years (streptococcal meningitis), showing a myelocyte with "toxic" granules in the cytoplasm and slight irregularity of the nucleus.

FIGURE VI.
Smear of sternal marrow from M.F., aged two years (streptococcal meningitis), showing a myelocyte with fewer "toxic" granules but more pronounced nuclear irregularity than in Figure V.

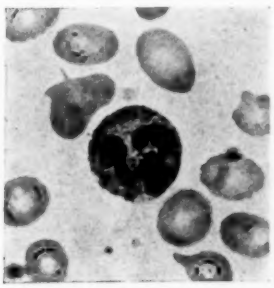


FIGURE VII.
Smear of sternal marrow from M.F., aged two years (streptococcal meningitis), showing a macropolycyte.

ILLUSTRATIONS TO THE ARTICLE BY DR. K. E. SHELLSHEAR AND DR. B. P. ANDERSON STUART.

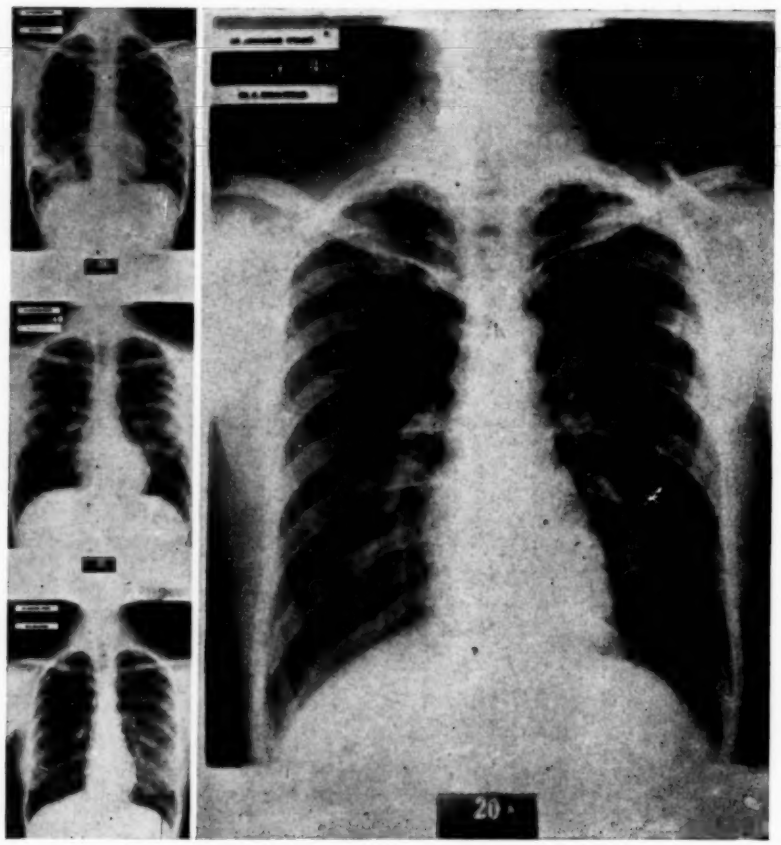


FIGURE I.

On the left is a strip of miniature films actual size; on the right is an enlargement.

16·9%, plasma cells 0·3%, megakaryocytes 0·2%, normoblasts 48·4%, and late erythroblasts 1·0%. Most of the cells of the neutrophilic series showed numerous "toxic" granules and pronounced variation in the nuclear outline. A few macropolycytes were present, but no vacuoles were seen. The sections also were very cellular, and a differential count gave similar figures: eosinophile cells 5·7%, neutrophile polymorphonuclear cells 0·2%, old metamyelocytes 1·2%, young metamyelocytes 5·4%, myelocytes 22·1%, premyelocytes 2·2%, myeloblasts 2·0%, monocytes 0·8%, lymphocytes 6·2%, mitotic figures 0·2%, megakaryocytes 0·9% and normoblasts 54·0%. In none of the specimens were toxic changes seen in the primitive red cells, nor were changes observed in the megakaryocytes.

Comment.

It was unfortunate that specific antipneumococcal serum was not available, for the synergism of antipneumococcal serum and sulphapyridine has been demonstrated by McLeod,[74] among others, and it may be that the serum acting with sulphapyridine would have converted the dramatic improvement which occurred after treatment for one week into a permanent cure. In view of the report by Scott and Meerapfel[75] that they were unable to obtain a suitable donor in their case owing to some change in the patient's blood as a result of sulphonamide therapy, it is interesting to observe that even when the blood sulphonamide level was 18·0 milligrammes per 100 cubic centimetres, there was no difficulty in cross-typing the blood of this patient. Also, even with this high blood sulphonamide level there was no change in the marrow which could not be explained by the severe and prolonged infection.

Toxic Changes in the Marrow Cells.

The presence of "toxic" granules in the cytoplasm of the neutrophile cells of the peripheral blood has been reported by Kugel and Rosenthal,[76] Sutro[77] and Bethell,[78] who conclude that the number and extent of the cells affected are related to the prognosis in the individual case. In this series of cases (Tables IA and IB), cytoplasmic "toxic" granules were numerous in the marrow cells from the patients with extensive pyogenic lesions, and it was observed that these granules were present to some degree at least in all the marrow specimens from these and other patients with infection, however mild. These "toxic" changes in the marrow were more extensive in the primitive cells than in the mature cells of the circulation, and Bethell's suggestion that in all probability the change occurs in the bone marrow, is confirmed.

The administration of sulphonamides did not apparently influence the occurrence of these "toxic" granules.

Macropolycytes.

In 1927 Cooke[79][80] first described the macropolycyte of the peripheral blood in pernicious anæmia and acute infections. This term, suggested by Rolleston, he applied to neutrophile cells with a diameter of more than 14μ, but he did not think there was any doubt that these cells began life in the blood stream as simple nucleated types. Cooke[81] divided the macropolycytes into three groups, according to variations in the structure of the nucleus and in the staining reactions of the granules of the cytoplasm. Since then the presence of macropolycytes in the peripheral blood in pernicious anæmia has often been confirmed; but the existence of these cells in the peripheral blood in acute infections has received but little attention. Kennedy and MacKay,[82][83] working in Iraq, observed macropolycytes in the peripheral blood in normal and pathological conditions other than pernicious anæmia and acute infections, and they suggested that the marrow stress was the result of the climatic environment.

In pernicious anæmia, changes in the granular series of the bone marrow were first reported in 1932 by Tempka and Braun,[84] who concluded that the pleomorphism of the nucleus, the copious granulation of the cytoplasm and the vacuolation of both the nucleus and the cytoplasm were all indicative of degeneration of the cells. Later, Jones[85] fully described the pleomorphic nuclei and other changes of the cells in every stage of neutrophilic development in the bone marrow in pernicious anæmia, and suggested that it was by means of those changes that the macropolycyte of pernicious anæmia developed in the marrow. Heck and Watkins,[86] Osgood and Young,[87] Nordenson,[88] Jones,[85][89] Jaffe,[90] and Dameshek and Valentine[91] have observed similar changes in the marrow in pernicious anæmia. Jones[85] concluded that the three types of macropolycytes described by Cooke were in reality morphological variants of the same pathological neutrophilic series, and in this paper I have not differentiated between the three types. These findings of Jones differ somewhat from those of Dameshek and Valentine,[91] who recorded maldevelopment only in the neutrophilic metamyelocytes and occasionally in myelocytes. Tempka and Braun[84] claimed that the macropolycytes were not specific for pernicious anæmia, having found them in the marrow of patients with carcinoma of the stomach, lymphogranuloma or myelogenous leuchæmia.

Although it is now universally agreed that the macropolycytes of the peripheral blood in pernicious anæmia are the results of the changes which occur in the developing neutrophile cells of the marrow, yet it is still undecided at what stage in the development of the neutrophile cells these changes first appear. The giant metamyelocytes or the "*grossere pathologische stabkernige Neutrocyten*" of Tempka and Braun, the multilobed adult neutrophile cells, alterations in the staining of the cytoplasm and variations in the shape of the nuclei of the premyelocytes and early myelocytes have been quite obvious in the marrow preparations from cases of pernicious anæmia which I have examined; but I have not been able to trace the pathological changes back beyond the premyelocyte stage to the myeloblast—that is, to the pregranular stage.

Macropolycytes have been discussed above in pernicious anæmia, in which condition they add to the evidence that the deficiency of the hæmatopoietic principle produces a panmyelopathy. As previously mentioned, Cooke[79] described the macropolycyte in the peripheral blood in pernicious anæmia and also in acute infections. These cells (Figure VII) have been present in the marrow from most of my patients suffering from acute infections; but in only one of this series (acute osteomyelitis of the femur) has it been possible to find them in the peripheral blood. That they do occasionally occur in the peripheral blood in acute infections there is no doubt, for they are sometimes seen while routine differential counts are being made on the peripheral blood. Thus it would appear that although the macropolycytes are often present in the marrow in severe acute infections, they are usually prevented from reaching the peripheral blood in these conditions in such numbers that they can be readily found.

No special function can be attributed to the macropolycytes in infection, and from a study of my material practically all the macropolycytes present seem to be adult cells of the metamyelocyte or polymorphonuclear leucocyte stage. It may be concluded that they are the result of changes occurring in cells at or before the metamyelocyte stage.

It has frequently been demonstrated that the deficiency of the hæmatopoietic principle in pernicious anæmia produces a panmyelopathy—that is, that the megakaryocytes and the developing white cells are also included in the pathological process. Fairley *et alii*[92] have shown that in tropical nutritional macrocytic anæmia, in which there is a deficiency of the extrinsic factor and therefore of hæmatopoietic principle, there are changes in all the elements of the marrow similar to those found in pernicious anæmia. Stasney and Higgins[93] have shown that in experimental cirrhosis of the liver cells resembling macropolycytes appear in the marrow and in the peripheral blood. Further, it is common knowledge that patients suffering from pernicious anæmia during both acute and chronic infections respond poorly to liver therapy, given orally or parenterally, but respond normally again when the infection subsides. This failure of response affects all the elements of the marrow. It would seem possible, when these facts are considered, that in acute infections an interference by the toxins with the metabolism of the hæmatopoietic principle in the liver occurs, with a resultant abnormal

development of some of the cells of the granular series, the process thus giving rise to the macropolycytes.

To return to the sulphonamides, it may be stated that in no marrow preparation from patients treated with these drugs were changes found in the macropolycytes, in number, structure or staining reactions of the cells, which differed from those in the marrow of patients with similar acute infections, but not receiving treatment with these drugs.

Nuclear Budding.

In addition to the alterations in the developing cells of the granular series which give rise to the macropolycytes, other nuclear variations in shape have been found in some acute infections. These appear as nuclear budding and as unequal partial division of the nuclei of the developing granular cells into two or more parts. These changes are illustrated in Figures I, II, III, V and VI. Although they are most pronounced in the neutrophilic series, these changes have been found to a less degree in nuclei of the cells of the eosinophilic series and very rarely even in cells of the basophilic series.

Various stages of nuclear budding are described by Cowdry[94] as occurring in cells in old tissue cultures in which other degenerative phenomena are present, and he states that these changes are especially apparent in fixed material. Figure VIII in the article by Galinowski[96] shows a premyelocyte with an irregular nucleus which has developed during the *in vitro* incubation of bone marrow cells with staphylococci. Recently, Israels,[99] working with *in vitro* cultures of marrow obtained by sternal puncture, has reported short grape-like protrusions of the cytoplasm of the myeloblasts after twenty-four hours; he states that on the second and third days the nuclei of the metamyelocytes become increasingly lobed and irregular in outline, and later the nuclei of the myelocytes become irregular but not lobed. The nuclear irregularities discussed by Galinowski and Israels would appear to be degenerative in origin and occur after many hours in culture. Isaacs[97] described alterations in the myeloid cells of the marrow after treatment with serum, and also a change in the surface tension of the cells, but he did not state how these surface tension alterations affected the cells.

The changes mentioned above as being present in the nuclei of the marrow cells from patients with acute infections, have been found by me only in smears prepared from marrow curettings emulsified in serum. On a few occasions smears of the marrow similarly prepared from patients with internal hæmorrhage or malignant disease, not associated with an infective process but with a peripheral leucocytosis, have contained these nuclear alterations. Because these changes have been found in smears from marrow emulsified in serum, but not in smears from aspirated material or in imprint preparations from the same patient, it may be concluded that these changes are artefacts and probably produced by alterations in the serum.

Be that as it may, it was found that these effects occurred more frequently in the marrow from patients with severe than in that from patients with mild infections. It was also found that the liability of the nuclei to undergo these changes was not related to the degree of leucocytosis of the peripheral blood. These variations have been found in biopsy as well as in post-mortem material, and although they were more frequent in the latter material, the liability of the nucleus to alter in serum is not entirely an agonal change. When possible, the serum used for the emulsification of the curettings has been the patient's own serum; in other cases the serum has been stock serum of the same group as the patient; yet in cases in which these nuclear abnormalities have not appeared on emulsification of the marrow in the patient's own serum, it has not been possible to produce these variations by allowing the marrow cells to stand in contact with stock serum of the patient's own group or of other groups. Neither the length of time that the cells were in contact with the serum nor the temperature of the serum while the emulsification was carried out (temperatures from 60° F. to 100° F. having been tried) appeared to influence the development of these nuclear abnormalities. Furthermore, I have not seen these changes in any supravital preparation. Rohr and Hafter[98] have shown that after death there is a gradual loss of lobulation of the nuclei of the marrow cells, so that when an hour has elapsed most of the cells appear to have small, round, regular, densely staining nuclei. The variations in the nuclei in my preparations developed in the few minutes that the cells were being emulsified and then spun in serum, and are therefore not comparable with alterations occurring in cell cultures or at some time after death.

These facts all confirm the conclusion that these changes in the outline and lobulation of the nuclei of cells of the granular series are due to an alteration in the serum which apparently takes place during the storage before use.

The "toxic" granulations, the vacuolation and the alterations in the staining reactions of the cytoplasm and of the nuclei, all of which changes are related to the actions of toxins on the cells, were seen in varying degrees in the marrow from patients with acute infections; but these toxic phenomena had no obvious relationship to the development of the nuclear abnormalities.

Alterations in the shape of the nuclei of the large mononuclear cells of the marrow have been seen by me in many conditions, but were greatest and most frequent in severe infections. Because these irregularities of the nuclei were seen in smears from aspirated marrow and in supravital preparations, it may be concluded that they were not artefacts and were different in origin from the variations occurring in the cells of the granular series.

These alterations in the cells of the granular series have been discussed in some detail because of their unexpected appearance in cells, some of which would have given rise to adult cells and others of which were adult cells and were destined to circulate in the peripheral blood as apparently normal blood cells. The cells of the peripheral blood failed to show these changes even when most of the marrow cells were so altered.

No relationship could be traced between this budding and partial division of the nuclei of the neutrophilic cells of the marrow and the administration of sulphonamides.

Giant Cells of the Marrow.

In addition to the well known megakaryocytes, large multinucleated giant cells with basophilic, foamy cytoplasm and six to 20 nuclei, were present in three of the 40 cases of this series (Figure IV). The nuclei were round or slightly oval, approximately 12μ in diameter and all of the same type—that is, the chromatin was loosely arranged with small lightly staining clumps; they possessed a definite nuclear membrane and bore no resemblance to the nuclear structure of the megakaryocytes. The nuclei formed approximately 50% of the cell volume and were scattered throughout the cell. A few of these giant cells had numerous platelets aggregated about the periphery. I have never seen similar cells in any other marrow specimens, whether my own or not.

Cells with these appearances have been found only in smears; in two cases the smears were prepared from emulsified curettings immediately after death (in one of these cases sulphapyridine had been administered); in the third case the smears were prepared from material aspirated during life, and this patient also had been treated with sulphapyridine. The diagnoses in these cases were, respectively, pneumococcal *empyema thoracis*, bronchopneumonia and streptococcal meningitis. In each of these cases there was a peripheral leucocytosis and the marrow was hyperplastic. The ages were one, ten and twenty-three years. In the two children the Mantoux test produced no reaction to dilutions of one in 1,000, but it was not performed on the third patient.

The consensus of opinion among the pathologists who have seen these specimens is that these cells are probably osteoclasts, with which I agree; but it must be noted that no part of the cytoplasm was eosinophilic, that no nucleoli were shown by the Romanowsky stains, and that they did not contain vacuoles or other particles in the cytoplasm (*vide* Dodds,[99] Arey[100][101] and Chang Hui Ch'uan[102]). One of these cells is illustrated in Figure IV. It will be

seen that the corner of the cell in contact with the myelocyte is stained darker than the rest of the cytoplasm, but it was still basophilic and not eosinophilic. The only reference I have been able to find which mentions multinucleated giant cells in human adult marrow is that of Jordon,[103] who described them in the femoral marrow of a patient suffering from typhoid fever, and who suggested that they were multiple hæmoblasts comparable to the blood islands of the yolk sac. Jordan, however, used fixed material and not smears, and was therefore unable to give a detailed description of their morphology.

From the appearance of these cells, they seem to have arisen by the division of one parent nucleus and not by the fusion of several cells.

Although I do not propose to enter into the controversy about the function of osteoclasts, it is interesting to observe that in these three cases there was a slight hyperplasia of the marrow as a result of the infection, but that in cases of leuchæmia and familial hæmolytic anæmia, in which the marrow hypertrophy was so great that widening of the medullary cavities of the bones occurred, I have been unable to find an increase in osteoclasts (or polykaryocytes).

It has already been mentioned that these giant cells have been found irrespective of the administration of the sulphonamides.

Sulphonamides in Leuchæmia.

Not because any hope was held that the sulphonamides would affect the course of leuchæmia, but because of a desire to test the efficacy of these drugs in this disease, I am reporting the results of the administration of sulphapyridine to four patients suffering from acute leuchæmia; in two cases it was lymphatic in type, in one myeloid and in the other probably monocytic.

The three points which suggested that the sulphonamides might beneficially affect the bone marrow in leuchæmia are as follows: (i) Sulphonamide therapy is sometimes associated with the development of a definite neutropenia or even agranulocytosis. (ii) It has been suggested that leuchæmia is due to an infecting organism. If this were so, then it is possible that the sulphonamides would interfere with the metabolism or multiplication of this organism. (iii) It has been shown by Lockwood and Lynch,[104] Gay *et alii*[105] and others that the sulphonamides exert a bacteriostatic action on many organisms without apparently interfering with the metabolism of the body cells. It was thought possible that these drugs might exert an inhibitory effect on the abnormal metabolism of the leuchæmic cells.

Each of the four cases was rapidly fatal, and in no case was any alteration observed in the clinical condition, the blood or the marrow which could be attributed to the sulphonamide therapy. (The fatal issue did appear to be hastened by the exhibition of the sulphapyridine.) Table II contains a summary of the findings in these four cases.

SUMMARY.

Most of the reported cases of depression of the bone marrow associated with sulphonamide therapy have been collected, and it is noticed that sulphanilamide was practically the only sulphonamide to be associated with the development of acute hæmolytic anæmia, that no case of acute hæmolytic anæmia has been reported to follow the use of sulphapyridine, and that in no case was "Uleron" administration related to the development of neutropenia. The marrow findings in those cases in which the marrow was examined are reviewed; and it appears that associated with the neutropenia of the peripheral blood there were a partial or complete disappearance of the adult granular cells of the marrow and an increase in the more primitive cells of the granular series, but no toxic changes have been described in these cells. In one case of anæmia and neutropenia toxic changes were described in the nucleated red cells; in the other two reported cases of hæmolytic anæmia associated with sulphonamide therapy, in which the marrow was described, there was slight hyperplasia of the nucleated red cells.

The case of a boy, aged three years, who died from pneumococcal meningitis, is reported; 159 grammes of sulphapyridine were given over a period of forty-two days, but death occurred. Apart from changes attributable to the infection, no abnormality was found in his marrow.

Marrow smears were examined from 20 patients treated with sulphonamides, and in no case was I able to find changes in the marrow cells, either qualitatively or quantitatively, which were not present in the marrow from a similar series of patients who had not received such treatment.

"Toxic" granules in the cytoplasm of the neutrophile cells in the marrow were observed in a varying degree, depending on the severity of the infection. These granules were more numerous in the cells at the myelocyte stage than in the mature cells.

Macropolycytes are discussed in pernicious anæmia and in infections. In pernicious anæmia changes were not found in the myeloblasts. Macropolycytes have been found in small numbers in the bone marrow of most patients suffering from acute infections who were examined; and yet, although they were present in the marrow of most of these patients, they were usually not released into the peripheral blood. It is suggested that the macropolycytes arise in infections from an interference by the toxins with the metabolism of the hæmatopoietic principle, and from a direct toxic effect on the cells. No variation, either qualitative or quantitative, was observed in the macropolycytes from the marrow of patients treated with sulphonamides when compared with those from similar patients without treatment.

Nuclear budding and partial division of the nuclei of the neutrophile cells and their precursors are described in marrow smears, but only when these were prepared from curettings emulsified in serum. These changes may represent a surface tension effect, and they were most numerous in the marrow from patients with severe infections.

Polykaryocytes, or large multinucleated giant cells, are described in the marrow of three patients with severe infections, and it is suggested that these cells were osteoclasts.

TABLE II.

Details of Patients with Acute Leuchæmia Treated with Sulphapyridine.

Diagnosis.	Age in Years.	Amount of Drug Used. (Grammes.)	Duration of Treatment. (Days.)	Leading Symptom.	Hæmoglobin Percentage.	Peripheral Blood.		Differential Count.		Result.
						Red Cells per Cubic Millimetre.	White Cells per Cubic Millimetre.	Blood.	Bone Marrow.	
Acute lymphatic leuchæmia.	10	19	2	Dyspnœa.	26	1,180,000	1,800	20% lymphoblasts	100% lymphoblasts	Death.
Acute lymphatic leuchæmia.	2	18	3	Otorrhœa.	32	1,900,000	4,200	92% lymphocytes	99% lymphoblasts	Death.
Acute myeloid leuchæmia.	42	8	1	Anorexia.	34	1,990,000	25,300	98% myeloblasts	98% myeloblasts	Death.
Acute monocytic leuchæmia.	22	7·5	2	Sore throat.	42	2,140,000	1,200	54% monocytes	30·6% monoblasts	Death.

For reasons given, sulphapyridine was administered to four patients suffering from acute leuchæmia, without the production of any alteration in the clinical condition, the blood, the bone marrow or the prognosis.

CONCLUSIONS.

1. Patients in whose peripheral blood the sulphonamides produced little or no effect, showed no alterations in the marrow attributable to the sulphonamide therapy.

2. In acute infections macropolycytes occur in the marrow more often than in the peripheral blood.

3. "Toxic" granules are more numerous in the myelocytes than in the mature neutrophile cells of the marrow in acute infections.

4. Nuclear abnormalities may occur in the neutrophile cells of the marrow during the preparation of smears from marrow curettings emulsified in serum.

5. Sulphapyridine does not appear to affect the course of acute leuchæmia.

ACKNOWLEDGEMENTS.

I am very grateful for the help and encouragement received from Professor P. MacCallum, of the University of Melbourne, and from the members of the honorary staffs and of the pathology departments of the Royal Melbourne Hospital, the Children's Hospital, Melbourne, and the Prince Henry Hospital, Sydney; and I wish to thank Mr. Wilkins, of the Prince Henry Hospital, who was responsible for the illustrations for this article.

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PHOTOFLUOROGRAPHY: THE USE OF THE MINIATURE FILM IN X-RAY DIAGNOSIS.[1]

By K. E. SHELLSHEAR, M.R.C.S. (England), L.R.C.P. (London),

AND

B. P. ANDERSON STUART, M.B., Ch.M., F.R.A.C.P.,
Sydney.

IN consequence of reports on the use of photofluorography in diagnosis in Germany and elsewhere, experiments were commenced in July, 1939, which finally demonstrated the efficiency of the method. Results were soon sufficiently far advanced to permit of a survey of the civil population at the request of Dr. J. Hughes, of the New South Wales Department of Public Health, Tuberculosis Division. This survey included tuberculous contacts and such members of the community as desired examination for the purpose of determining their freedom from pulmonary tuberculosis.

The objects of this communication are to place on record the result of the examination of 1,000 consecutive subjects, and to describe for the guidance of others the technical aspects of the method and its difficulties. At the outset it is necessary to emphasize that, whilst many pulmonary conditions may be diagnosed, the great usefulness of this method at the present time is in mass survey work for the detection of pulmonary tuberculosis. Despite the small loss of detail occasioned by two factors yet to be overcome (the grain of the film and the grain of the screen), our results make the comparison of the miniature film with the large film a very satisfactory one, although the miniature film cannot entirely replace the large film in the minute detailed examination of the chest. However, any

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disadvantage of the miniature film is more than counterbalanced by the large numbers of subjects who can be effectively dealt with, since the difficulties of examining the same numbers with the large film are insurmountable.

Photofluorography opens up a new avenue of examination to the wage-earning class. Low cost is not the only advantage. Appointments can be made by those conducting the survey without interference with working hours. It was found that the most convenient hours were between 5 and 7 in the evening; and the organization should be such that the attendance of each patient is only a matter of minutes.

In the estimation of the cost of a mass survey, every item must be taken into consideration. Published estimates are far too low, and have apparently been given without sufficient knowledge of the procedure. The cost of the film itself is negligible. The cost of a survey must include the salaries of a large technical and clerical staff in addition to the capital outlay and maintenance of a powerful X-ray machine and a photofluorographic apparatus. Apart from this, provision should be made for adequate remuneration for highly specialized medical service.

Whilst the analysis of the 1,000 cases dealt with is the matter of primary importance, it is convenient to discuss technical details first. The photographic apparatus was designed along the lines suggested in Siemens's brochures then available. Equipment of similar design was published by Manoel de Abreu;[1] similar equipment, designed by I. Seth Hirsch and Myron Schwarzschild, is also in regular use at the Beth Israel Hospital, New York. The apparatus will therefore not be described in full detail.

The essential parts of the apparatus are an X-ray unit and a photographic unit. The X-ray unit should be capable of delivering at least 80 milliampères at 100 kilovolts. It does not matter what it is capable of delivering in the manufacturer's factory or catalogue; it must deliver 80 milliampères across the X-ray tube with the line supply where it is to be used. It is, of course, desirable to have a reserve power above this; anything lower would militate against efficient results. The machine in use by us is a "Watson Premier" with four-valve rectification capable of an output of 500 milliampères at 100 kilovolts. A six-kilowatt heavy anode tube was found to be most suitable. The rotating anode tube is not suitable for mass survey examinations, owing to excessive wear on the rotating mechanism, and also the high cost of replacements.

The photographic unit consists of a miniature camera fitted with a 1·5 lens and a fluoroscopic screen enclosed in a lightproof box. This camera takes the 35-millimetre film. No supernumerary lens is added, because the use of such lenses might tend to upset optical values. The essential factor is that the lens must be capable of covering the screen without loss of detail or illumination on the margins. The focal distance required to cover the screen fully is 88 to 90 centimetres. Focusing is accomplished by the use of spacing rings between the camera and the lens. In accordance with the advice of Dr. C. E. Eddy, of Melbourne, optical lead glass was placed in front of the lens as a precaution against damage to it by the rays. As a result of this, no loss of efficiency has been noted either in detail or in light value. Owing to the bright fluorescence of the screen, the interior of the box must be lined with black cloth to prevent reflected images. The focusing is so delicate that once it is correctly obtained, the camera should be so fixed that the film can be changed without its being moved from its position.

A Heydon or Levy-West screen of the fast zinc sulphide type is equally effective. Some experiments carried out with a new "Patterson Blue" screen seemed to indicate that it was designed to give its maximum intensity with a low kilovolt and a high milliampère technique.

In mass surveys it is imperative to ensure that there is no possibility of error in the identification of films. In the mass survey of troops in Germany, the record card of the person examined was inserted into the machine when he came to it. The relevant information was photographed on the film before the X-ray exposure was made, and the card was returned to him after the examination. The principles of this method were adopted by us. The apparatus consists of an illuminating chamber so affixed to the main box of the photographic unit that a card slid into it can be photographed by reflected light from a miniature globe. During the exposure of the card a second external globe, in series with the globe in the machine, lights up. This ensures that the system is working and also acts as a signal to the operator that everything is ready for the X-ray exposure. In the whole series no doubt existed at any time as to the identity of the patient who was the subject of the film. A further advantage of this method, apart from the possibility of confusion, is that there is no loss of time.

Kodak super-panchromatic "XX" film has been used exclusively. Recently the Eastman Kodak Company, of New York, has produced two special types of film for use in photofluorography. One of these is blue sensitive film for use with the Patterson "Special Fluorazure" screen—a screen from which the tinted over-coating has been omitted. The other is a green sensitive film for use with a green fluorescent screen, such as the Levy-West or Heydon screen. We have just received samples of both these films through the courtesy of the Eastman Kodak Company, and we intend to carry out tests without delay. It is recommended that both types of film should be developed in Eastman Kodak X-ray developer for five minutes. This short developing time would in itself be a great advantage. The blue sensitive film may be handled under ordinary X-ray safe lights in the processing procedure. However, inasmuch as the green sensitive film is highly orthochromatic, a "series 2" Wrattan safe light should be used and the film should be exposed to this light as little as possible in handling. Prior to the exposure the shutter of the camera is opened. The timing is determined by the X-ray exposure and the resulting fluorescence of the screen. In this survey the numbers examined have not reached such proportions that great speed of operation was necessary, and no attempt was made to classify the subjects before examination into groups of equal size, as has been done elsewhere. The rate never exceeded 60 per hour, because there were mixed sex groups treated as private patients, and individual estimation of exposure was found to be more convenient. For guidance the following approximate figures are given: for an average subject the exposure is 90 to 100 kilovolts, 80 milliampères for eight twentieths to ten twentieths of a second when a micro-grid is used, and 80 to 90 kilovolts, 80 milliampères for four twentieths to five twentieths of a second without the grid.

Experiments were made with many different types of developer. Most of our work has been done with Kodak D76. Development temperature was 67° F. with a developing time of one hour. Recently we have used "Kodalk X-ray Developer", with seven minutes' developing time at a temperature of 66° F. This has given excellent results, the films being free of grain and having good contrast. We have found the short developing time much more convenient.

The temperature of the solutions must be kept constant throughout the processing. Experience in handling this film proves that no detail can be neglected. After the washing, the films should be wiped down with a wet chamois leather and dried with a small weight on the end of the film to prevent curling. The films must be thoroughly dry, otherwise moisture collects on the glasses of the projector, causing it to adhere to the glass. The films should not be projected more often than necessary because of the liability to scratching. This, however, can be partly overcome by coating the films with clear "Duco", or in special cases by mounting the films separately in small glass holders.

Throughout our preliminary experiments, and practically to the end of the survey, one of our outstanding problems was the maintenance of good contrast in the films. Close attention to details of developing technique gave better results; but it was felt that the elimination of secondary rays gave scope for further improvement. In Siemens's catalogue a micro-grid was mentioned as having been used. Our initial experiments with grids were not

satisfactory, owing to loss of light values on the margins of the films. It was only towards the end of the survey, when a Siemens's focused micro-grid became available, that this difficulty was finally surmounted and a high degree of contrast was obtained. This, however, necessitated the increasing of the exposure nearly three times. In miniature film work, when zinc sulphide screens are used, the kilovoltage appears to have less influence on the degree of contrast than in ordinary radiography. Contrary to expectation, no diminution of contrast occurred when the kilovoltage was raised even to 100 to permit of a more rapid exposure. When the focused grid is used, correct alignment of all units is essential.

The position in which the patient is placed in photofluorography is similar to that in ordinary radiography; but since the alignment of the tube and grid permit of no variation, special care must be taken to ensure the correct centring of the patient and to obtain the full view of the apices of the lungs.

The examination of the films may appear to be the least difficult part of photofluorography; but we found that satisfactory viewing of the films presented many difficulties. Standard projection apparatus is not entirely suitable. A projector of high power with a photographic lens, preferably of long focal length, gives the best results. Many types of viewing screens have been tried, the most satisfactory being a smooth white matt surface. A Patterson intensifying screen is excellent for the purpose. Those who are accustomed to using only ordinary viewing boxes may prefer to view the pictures through opal glass. Care should be taken to project the picture onto the flashed side. The film is reversed in the projector and the image is viewed through the glass from the opposite side. We have tended to make the projections smaller as our work has progressed, preferring ten inches by eight inches or even less.

Our analysis of results cannot be regarded as a true index of the incidence of pulmonary tuberculosis in the population, because many subjects were contacts and some were even known to be suffering from pulmonary tuberculosis. The greater number presented themselves, however, on account of the growing tendency of the general public to be better educated in health matters. Patients in whom any pathological lesion was discovered were referred back to the medical officer of the Tuberculosis Division of the Department of Public Health, who arranged for their treatment whenever possible by their own medical attendant. Ages ranged from infancy to old age, by far the greater number of subjects being young adults.

At the outset it was deemed advisable to make a reexamination by the ordinary methods of radiography in all pathological or doubtful cases. In no case was it found necessary to alter the diagnosis arrived at. Latterly reexamination has been made only when a large film is required for some special reason.

For this report a simple classification is adopted. This broad classification is used merely for simplicity in this communication, but when the report in each case was made, full details were of course given with regard to the site and extent of the involvement, and the presence or absence of cavitation, fibrosis *et cetera*. The classification, and the results of examination of 1,000 subjects, are as follows:

Class.		Number of Subjects.	Percentage.
1. Normal		878	87·8
2. Tuberculosis, active		47	4·7
(*a*) Early	16	1·6	
(*b*) Moderately advanced	19	1·9	
(*c*) Advanced	12	1·2	
3. Tuberculosis, healed		33	3·3
4. Other lesions		42	4·2
Pleural thickening	16		
Cardiac enlargement	8		
Aortic enlargement	1		
Marked bronchitic changes	9		
Bronchiectasis	4		
Unresolved pneumonia	1		
Hydatid disease of the liver	1		
Diaphragmatic hernia	1		
Pneumonokoniosis	1		

Some of the above subjects had advanced lesions, and in consequence were a menace to the community; others were discovered with lesions in the early stages, when treatment could offer the most benefit.

The result of the survey up to date cannot fail to demonstrate that photofluorography is a notable advance in the campaign against tuberculosis.

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PHOTOFLUOROGRAPHY.[1]

By HOWARD B. GOUGH, Assoc.I.E.E.,
Sydney.

EQUIPMENT was recently available in Sydney for making photofluorographs on both four inches by five inches and 35 millimetres film, and an offer was made to the Radiological Association that, should the association care to take advantage of this, a series of photofluorographs and check radiographs on 17 inches by 14 inches film could be made of a group of patients for comparison purposes as to their diagnostic value. The Radiological Association accepted the offer and approached the Board of the War Memorial Hospital, Waverley, with a view to obtaining permission for the work to be carried out in the X-ray department of that hospital, where a modern, high-power, four-valve diagnostic machine was recently installed. The Board graciously gave its consent, and thereupon the necessary additional apparatus, including the photofluorographic units, was installed.

The high-tension generator is a four-valve plant capable of delivering an output up to 500 milliampères. For controlling the time of exposure two timers were available; one was of the impulse type, with which exposure times from 1/100 to 24/100 of a second in intervals of 1/100 of a second could accurately be obtained, and the other was a synchronous motor timer which was used for exposure times over 24/100 of a second. The generating equipment, therefore, admirably met the energy requirements for photofluorography—namely, 40 to 80 milliampère seconds at 65 to 75 kilovolts peak and 44 inches focal screen distance.

The X-ray tube employed was a double focus rotating anode Coolidge tube. The focus having an effective area of two millimetres was selected for all the radiographic and photofluorographic work.

The four inches by five inches photofluorographic unit incorporates a special 14 inches by 17 inches fluorescent screen, and an *f* 1·5 photographic lens in a light-tight assembly mounted on a supporting structure providing easy vertical adjustment to suit the height of the patient. The fluorescent screen is mounted in the front of the assembly with the lens, focusing device and film holder at the rear. The special *f* 1·5 lens is a six-element cemented type, 150 millimetres (about six inches) in diameter, and weighs approximately 26 pounds.

As will be appreciated, with a lens of this type focusing is critical to a fraction of a millimetre. The adjustment is made by varying the lens holder position by means of a fine threaded screw. The method of focusing is to make photofluorographs of a wire mesh mounted immediately in front of the fluorescent screen holder. Successive photofluorographs are made each with an alteration of one half-turn of the adjustment screw until the optimum focus has been obtained. Once this is found, the screw is locked and the unit remains in focus indefinitely.

In order to minimize the effect of motion, exposure times should be as short as possible. One of the factors bearing on this desirable end result is that the fluorescent screen should have a high actinic light output when energized by X-rays. To meet requirements, a special fluorazure fluoroscopic screen has been developed, the fluorescent

[1] Read at a meeting of the Australian and New Zealand Association of Radiology on October 18, 1940, at Sydney.

chemical of which is prepared with an unusually high active power in the blue. The spectral distribution of this screen is from 4,200 to 5,300 Ångström units, the maximum band lying between 4,200 and 4,900 Ångström units.

The type of film most effective with this screen at present appears to be the regular double-coated X-ray emulsion film processed in standard X-ray developer and fixer. The lead glass protecting the lens and film is ground and polished, free from bubbles, scratches, wavy areas *et cetera* to avoid interference with, or distortion of, the fluoroscopic image.

For the making of photofluorographs the patient is placed in position and handled in the same manner as for the making of a 14 inches by 17 inches radiograph. The four inches by five inches negative of the image appearing on the special fluorescent screen is produced photographically when the X-ray exposure is made. The technique employed for the four inches by five inches photofluorographs was 400 milliampères at 44 inches' distance, the kilovoltage and time being varied according to the thickness of the patient. (The time was 3/20 of a second at 66 to 76 kilovolts peak for chests 18 to 23 centimetres in thickness.) The chest thickness of each patent was measured with calipers.

These techniques should not be regarded as invariable, for some observers prefer a greater or less degree of density. A series of four inches by five inches photofluorographs was therefore made of exposure values in respect to kilovoltage and time, either side of those nominated above being used.[1]

The objective in the development of the four inches by five inches unit was the production of a photofluorograph small enough to result in real economy in film through its use yet large enough to permit interpretation by direct visual examination (or at least with no greater enlargement than that produced by a reading glass). Radiologists abroad who have made some thousands of four inches by five inches photofluorographs have given their opinion that this objective has been achieved. Question has been raised as to whether satisfactory photofluorographs may be made with X-ray equipment of lower power than that which was used in our series of experiments. Lower energies may be used, providing the user is prepared to extend the exposure time or decrease distance in order to obtain adequate density. Increased exposure time, however, may decrease the detail of the chest somewhat, for it introduces a possibility of movement of the patient and of cardiac motion. Decrease in distance will cause geometric enlargement, particularly in the posterior region, and this also decreases detail. The degree of acceptable quality loss varies with individuals; but if nothing less than the best possible quality is acceptable, then at the present development of X-ray science high-power equipment and a rotating anode tube should be considered essentials.

For the purpose of studying the effect in resultant definition of image when varying tube-screen distances and various target effective focal areas are used, and also for the purpose of checking sharpness of focus of the photofluorographic units (both four inches by five inches and 35 millimetres), a phantom was constructed consisting of wires stretched in a frame, each wire being spaced one inch from its neighbour in respect to depth, so that when placed in position in the front of the fluorescent screen of the photofluorographic unit the nearest wire was one inch from the screen and the remaining wires in turn were distant each a further one inch, up to a total of ten inches. Each wire was numbered for identification purposes by small split lead shot fixed on it, the inner lead shot on each wire being equidistant from the centre of the phantom. The wires at the one-inch screen distance in addition carried a lead disk about one inch in diameter, and those at the ten-inches distance an annular ring. The inside diameter of the latter was somewhat larger than that of the disk. Therefore, if the tube position was adjusted so that the shadow of the disk appeared immediately in the centre of the ring as viewed on the fluorescent screen, the tube would be accurately centred.

[1] These photofluorographs were presented to the meeting for inspection.

Photofluorographs made with this phantom by means of a tube having an effective focal area of two millimetres or less and a target-screen distance of 44 inches or more did not display to the unaided eye any differences in resultant definition. When a tube was used with a focal spot of the order of four millimetres effective and distances of 30 to 36 inches, the gradual loss of definition from wire number 1 to wire number 10 was clearly perceptible. Furthermore, these test pictures clearly indicate the increased distortion, as evidenced by the difference in distances X and Y (Figures IA and IB), as the focal screen distance is reduced. Note also progressive loss of definition from wire number 1 to wire number 10 in Figure IB.

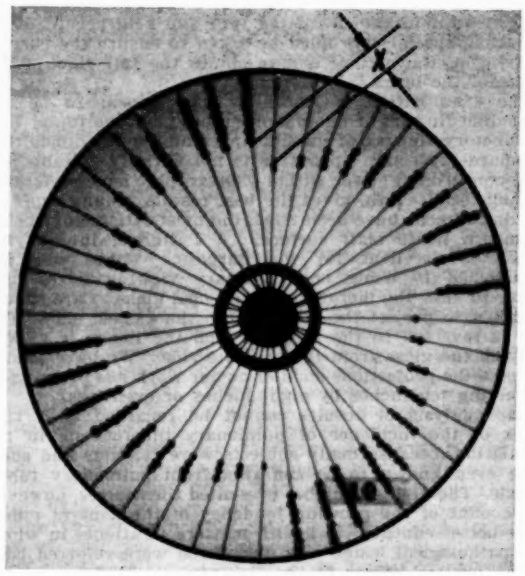

FIGURE IA.
Tube/screen distance 48 inches. Effective focus of X-ray tube 1·5 millimetres.

The 35 millimetre photofluorographic unit used in the series of experiments is similar in general construction to the four inches by five inches unit, but is arranged to accommodate a standard 35 millimetre miniature camera fitted with an *f* 1·5 lens. The fluorescent screen is a standard Levy-West zinc sulphide screen, which fluoresces a greenish-yellow colour, this colour being especially suited to the well-known fine grain cinematograph films.

In order to determine the technique for 35 millimetre photofluorography, a series of exposures at various kilovoltages, milliampèrages and exposure times was made of a number of patients of different chest thicknesses. The photofluorographs were then examined by a number of observers for the purpose of selecting the best photofluorograph of each of the patients, irrespective of the technique employed—which in any case was not disclosed until the selection had been made. The qualities considered as being the most desirable were sharpness of definition and contrast. When the final choice was made it was found that the photofluorographs selected had all been made at 60 kilovolts peak, the variant in respect to thickness of patient being exposure time. A technique chart was then prepared from the data thus obtained. All the 35 millimetre photofluorographs which will be shown later, therefore, were made at 400 milliampères, 44 inches tube-screen distance, 60 kilovolts peak for the male patients and 64 kilovolts peak for female patients, at times of exposure to suit the thickness of the patient. (One-tenth to one-fifth of a second for chests 18 to 23 centimetres in thickness.) A Bucky screen grid was not used. Some test photofluorographs were made with a Bucky screen grid, but whilst there was some gain in contrast, there appeared

to be a loss of sharpness of definition. Furthermore, the use of a Bucky screen grid demands a greater amount of energy or longer exposure time. However, the Bucky screen grid may possibly prove a useful accessory, particularly when only comparatively low power plant is available and high kilovoltages have to be used to obtain the requisite density. This is being made the subject of further investigation.

The technique employed in the making of the 17 inches by 14 inches check radiographs was 400 milliampères, 72 inches distance, one-twentieth of a second, and kilovoltage according to the patient's chest thickness, 54 to 64 kilovolts peak for chests 18 to 23 centimetres in thickness.

In the literature on the subject of photofluorography many references have been made to the saving in cost which can be effected if this method is utilized for group chest surveys. In fact, saving of expense is, of course, the main object of photofluorography.

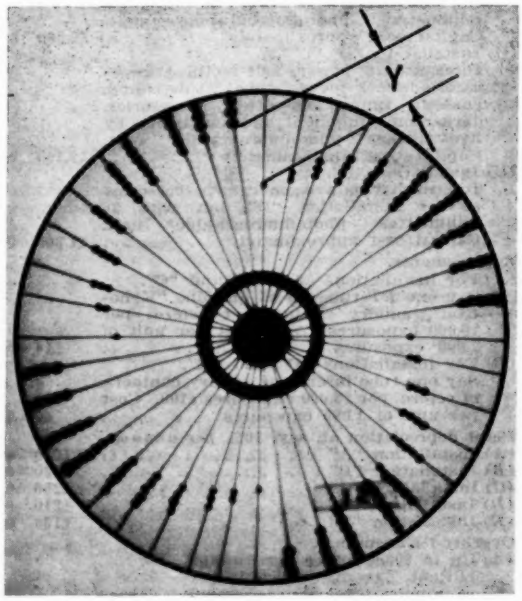

FIGURE IB.
Tube/screen distance 30 inches. Effective focus of X-ray tube 3·8 millimetres

Mostly references to cost have been in regard to the photographic materials used; but to obtain a proper perspective of cost, consideration must be given to moneys expended on such things as the maintenance of equipment, replacements (especially X-ray tubes and vacuous devices), depreciation of plant, overhead charges such as rent of premises, cleaning, laundry, wages of technicians, nurses, ushers, clerical assistants *et cetera*. It should also be remembered that a certain percentage of photofluorographic examinations are repeated on 17 inches by 14 inches sheet film, the cost of which must be spread over the total number of patients examined.

With these thoughts in mind, some calculations were made with the idea of learning something of the approximate cost per case when the various types of equipment and methods were utilized. The findings which are given in the appendix (and graphically in Figures II and III) were shown to your President (Dr. A. T. Nisbet), who found them of such interest that he invited me to place them before you this evening. For the purpose of these calculations, it has been assumed that a clinic for group chest survey work only, is to be established, and will need to be equipped and staffed for that purpose. Certain of the factors which have been assumed may be open to

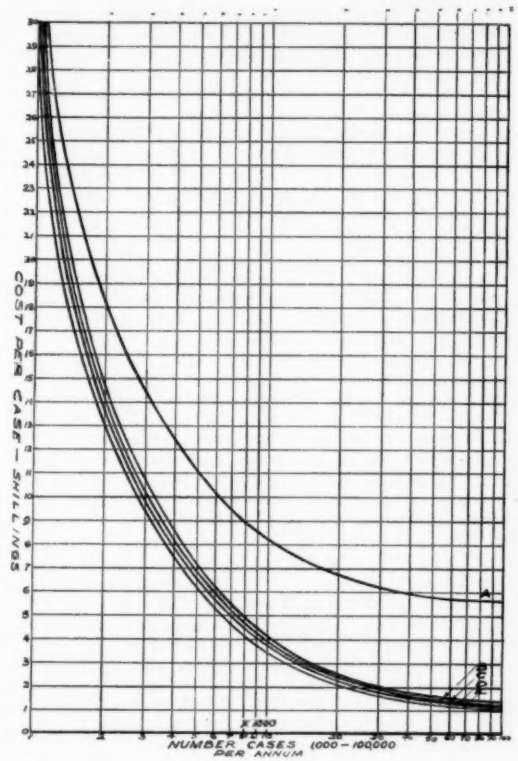

FIGURE II.

criticism or correction; but when assumptions have been made an average figure was used, calculated after conversations with radiologists and others who have had experience with these matters. For comparison, costs associated with examinations by direct radiographs on 14 inches by 17 inches film also are given.

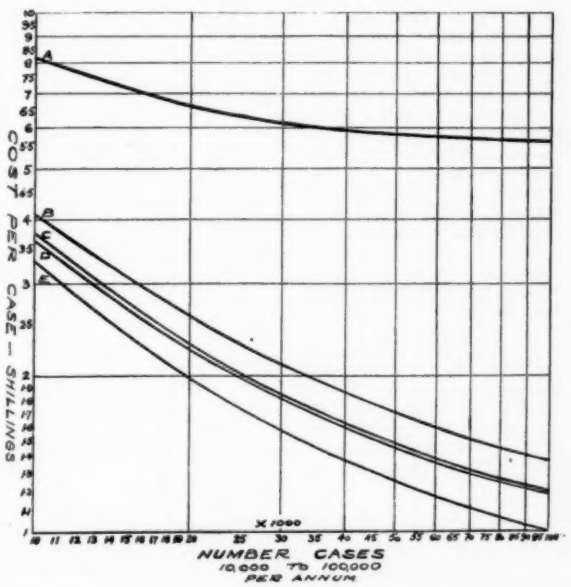

FIGURE III.

In order to determine the amount of money to be allowed for depreciation of plant, which can be considered to be 10% *per annum* of the capital outlay, the first item of cost for consideration is that of equipment. As far as the energizing unit is concerned two main types have been employed—namely, (i) the high-power four-valve diagnostic apparatus having an output of, say, 500 milliampères, and (ii) that having an output of the order of 100 milliampères, incorporating a self-rectified X-ray tube. Approximate costs of various combinations of equipment are given in the appendix under the headings of installations "A", "B", "C", "D" and "E".

The next item is that of replacements—particularly vacuous devices. It is considered that for the high-powered installation a conservative estimate would be £14 and for the intermediate installation £5 per unit of one thousand exposures. In addition, amounts must be included for the routine servicing of the plant, for usable materials such as films, chemicals and electricity, and for spoilage due to technical errors. For 17 inches by 14 inches sheet film work only, the cost for the materials would amount to £243 per unit of one thousand exposures; for five inches by four inches film the cost for materials per unit would be £30, including 1% of "retakes" on 17 inches by 14 inches film; and for 35 millimetres film the cost for materials, including 6% of "retakes" on 17 inches by 14 inches film, would be £22.

It is somewhat difficult to assess overhead expenses, since obviously as the number of patients examined *per annum* increases more staff will be required. It has been assumed, therefore, that for the examination of up to 30,000 patients *per annum* four workers would be adequate—namely, one technician, one usher, one clerk and one dark-room assistant. From 30,000 to 70,000 patients *per annum* two additional workers would be required, a total of six; and from 70,000 to 100,000 patients *per annum* three further workers would be required, a total of nine. The total overhead expenses for up to 30,000 cases would be approximately £1,275, from 30,000 to 70,000 cases £1,710, and from 70,000 to 100,000 cases £2,145. In practice some of the factors might vary by quite an appreciable percentage from the assumed figures; but even so, the cost per patient would not be greatly affected if the number of patients examined *per annum* exceeded 25,000.

If an existing installation of a high powered type with which, say, some 3,000 cases of a general nature are dealt with *per annum*, is to be used also for group chest survey work, the cost per chest case will differ from that of a clinic devoted to survey work only, as overhead expenses have to be shared. In such circumstances, if 500 cases over the standard quantity of 3,000 were dealt with each year, the cost per case would be 13·16 shillings, falling to 8·64 shillings each if 5,000 cases were dealt with. On five inches by four inches film the figures respectively would be 9·48 shillings and 4·65 shillings, whilst on 35 millimetres film the figures would be 8·92 shillings and 4·31 shillings (Figure IV).

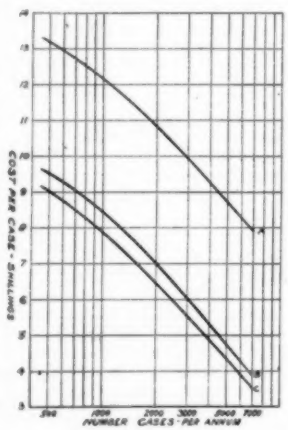

FIGURE IV.

Acknowledgements.

The author wishes to thank the directors of Messrs. Watson Victor, Limited, for permission to publish the information contained in this paper, and acknowledges his indebtedness to Mr. L. E. Burt, A.M.I.E.E. (Australia), and Mr. J. G. O'Brien, F.O.A., for valuable assistance in connexion with the work described.[1]

Appendix.

Group Chest Surveys: Comparative Costs.

1. Radiographs on 17 inches by 14 inches sheet film.
2. Photofluorographs on five inches by four inches film.
3. Photofluorographs on 35 millimetres film.

1. Equipment.				
(*A*) Installation "A". Four-valve high-power generator, impulse and synchronous timers, rotating anode tube, tube-stand, cassette tunnel, cassettes, accessories and dark-room equipment. Capital cost approximately ..			£2,300	0 0
(*B*) Installation "B". As installation "A", but including four inches by five inches photofluorographic unit. Capital cost approximately			£3,300	0 0
(*C*) Installation "C". As installation "A", but including 35 millimetres photofluorographic unit. Capital cost approximately			£2,500	0 0
(*D*) Installation "D". Intermediate power, self-rectified generator, shock-proof tube, tube-stand, cassette tunnel, cassettes, accessories, dark-room equipment, and four inches by five inches photofluorographic unit. Capital cost approximately			£2,100	0 0
(*E*) Installation "E". Intermediate power generator, accessories as for installation "D", but with 35 millimetres photofluorographic unit. Capital cost approximately			£1,300	0 0
2. Replacements.				
(*A*) For installations "A", "B" and "C". Say one *RT* tube insert and one "Kenotron", sundry contacts *et cetera*, per 20,000 exposures £280. Cost per unit of 1,000 exposures			£14	0 0
(*B*) For installations "D" and "E". Say one tube insert and sundry contacts, *et cetera*, per 20,000 exposures £100. Cost per unit of 1,000 exposures			£5	0 0
3. Plant depreciation at, say, 10% *per annum*.				
(*A*) Installation "A"			£230	0 0
(*B*) Installation "B"			£330	0 0
(*C*) Installation "C"			£250	0 0
(*D*) Installation "D"			£210	0 0
(*E*) Installation "E"			£130	0 0
4. Overhead Expenses.				
(*A*) Up to 30,000 cases *per annum*.				
1. Rent rooms, cleaning, laundry, telephone and sundries, say	£350	0 0		
2. Wages: one technician, one usher, one clerk, one dark-room assistant (four workers in all), say ..	£900	0 0		
3. Routine servicing of plant, say	£25	0 0		
			£1,275	0 0
(*B*) From 30,000 cases *per annum* to 70,000 cases *per annum*.				
1. Rent rooms *et cetera*, say	£375	0 0		
2. Wages: two technicians, one usher, two clerks, one dark-room assistant, (six workers in all), say ..	£1,300	0 0		
3. Routine servicing of plant, say	£35	0 0		
			£1,710	0 0
(*C*) From 70,000 cases *per annum* to 100,000 cases *per annum*.				
1. Rent rooms *et cetera*, say	£400	0 0		
2. Wages: three technicians, two ushers, two clerks, two dark-room assistants (nine workers in all), say	£1,700	0 0		
3. Routine servicing of plant, say	£45	0 0		
			£2,145	0 0

[1] The reading of the paper was followed by a demonstration of four inch by five inch and 35 millimetre photofluorographs, with check radiographs on 17 inches by 14 inches film; both normal and pathological conditions were illustrated.

5. Usable material *et cetera* per unit of 1,000 cases.

(*A*) Seventeen inches by fourteen inches sheet film only.

1. Films	£225 0 0	
2. Chemicals	£12 10 0	
3. Electricity	£0 5 0	
4. Spoilage and repeats, say	£5 5 0	
		£243 0 0

(*B*) Five inches by four inches film.

1. Films	£25 0 0	
2. Chemicals	£1 5 0	
3. Electricity	£0 5 0	
4. Spoilage and repeats, say	£0 10 0	
	£27 10 0	
Retakes on 17 inches by 14 inches film (say 1%).		
1. Films 2. Chemicals 3. Electricity	£2 10 0	£30 0 0

(*C*) Thirty-five millimetres film.

1. Films	£6 5 0	
2. Chemicals	£1 0 0	
3. Electricity	£0 5 0	
4. Spoilage and repeats, say	£0 5 0	
	£7 15 0	
Retakes on 17 inches by 14 inches film (say 6%)	£14 5 0	£22 0 0

6. Cost per case with various installations and with varying numbers of cases.

(*A*) Installation "A", high-power generator and all 17 inches by 14 inches film.

Cases.	Materials and Replacements.	Overheads and Depreciation.	Total (£).	Case per Case (Shillings).
1,000	257	1,505	1,762	35·24
5,000	1,285	1,505	2,790	11·16
10,000	2,570	1,505	4,075	8·15
30,000	7,710	1,940	9,650	6·43
70,000	17,990	2,375	20,365	5·82
100,000	25,700	2,375	28,075	5·61

(*B*) Installation "B", high-power generator and four inches by five inches photofluorographic unit.

1,000	44	1,605	1,649	32·98
5,000	220	1,605	1,825	7·30
10,000	440	1,605	2,045	4·09
30,000	1,320	2,040	3,360	2·24
70,000	3,080	2,475	5,555	1·58
100,000	4,400	2,475	6,875	1·37

(*C*) Instalation "C", high-power generator and 35 millimetres photofluorographic unit.

1,000	36	1,525	1,561	31·22
5,000	180	1,525	1,705	6·82
10,000	360	1,525	1,885	3·77
30,000	1,080	1,960	3,040	2·02
70,000	2,520	2,395	4,915	1·40
100,000	3,600	2,395	5,995	1·19

(*D*) Installation "D", intermediate generator and four inches by five inches photofluorographic unit.

1,000	35	1,485	1,520	30·40
5,000	175	1,485	1,660	6·64
10,000	350	1,485	1,835	3·67
30,000	1,050	1,920	2,970	1·98
70,000	2,450	2,355	4,805	1·37
100,000	3,500	2,355	5,855	1·17

(*E*) Installation "E", intermediate generator and 35 millimetres photofluorographic unit.

1,000	27	1,405	1,432	28·64
5,000	135	1,405	1,540	6·16
10,000	270	1,405	1,675	3·35
30,000	710	1,840	2,550	1·70
70,000	1,790	2,275	4,065	1·16
100,000	2,700	2,275	4,975	0·99

Cost of group survey work when an existing installation is utilized which plant is used for 3,000 cases *per annum* other than the group chest surveys.

7. Equipment.

(*A*) Installation "A". High-power diagnostic equipment, accessories, dark-room equipment, furniture and fittings. Capital value, say		£3,000 0 0
(*B*) Installation "B". High-power diagnostic equipment *et cetera* as installation "A", but in addition a five inches by four inches photofluorographic unit. Capital value, say		£4,100 0 0
(*C*) Installation "C". High-power diagnostic equipment *et cetera* as installation "A", but in addition a 35 millimetres photofluorographic unit. Capital value, say		£3,350 0 0

8. Replacements (tubes *te cetera*).

As per item 2 (*A*), per 1,000 cases	£14 0 0

9. Plant Depreciation at, say 10% *per annum*.

(*A*) Installation "A" [Item 7 (*A*)]	£300 0 0
(*B*) Installation "B" [Item 7 (*B*)]	£410 0 0
(*C*) Installation "C" [Item 7 (*C*)]	£335 0 0

10. Overhead expenses.

(*A*) Rent of rooms, cleaning, laundry, telephone *et cetera*, say, *per annum*	£375 0 0	
(*B*) Wages staff: technician, nurse and clerk, say, *per annum*	£700 0 0	
(*C*) Routine servicing plant, say, *per annum*	£25 0 0	
		£1,100 0 0

11. Usable material (per 1,000 cases).

(*A*) With 17 inches by 14 inches sheet film [as Item 5 (*A*)]	£243 0 0
(*B*) With five inches by four inches film [as Item 5 (*B*)]	£30 0 0
(*C*) With 35 millimetres film [as Item 5 (*C*)]	£22 0 0

12. Cost per case for group chest examination.

Chest Cases.	General Cases.	Total.	Material and Replacements.	Proportion Overhead Expenses and Depreciation.	Total (£).	Cost per Case (Shillings).
(*A*) On 17 inches by 14 inches film.						
500	3,000	3,500	129	200	329	13·16
1,000	3,000	4,000	257	350	607	12·14
2,000	3,000	5,000	514	560	1,074	10·74
5,000	3,000	8,000	1,285	875	2,160	8·64
(*B*) On five inches by four inches film.						
500	3,000	3,500	22	215	237	9·48
1,000	3,000	4,000	44	377	421	8·42
2,000	3,000	5,000	88	603	691	6·91
5,000	3,000	8,000	220	944	1,164	4·65
(*C*) On 35 millimetres film.						
500	3,000	3,500	18	205	223	8·92
1,000	3,000	4,000	36	359	395	7·90
2,000	3,000	5,000	72	574	646	6·46
5,000	3,000	8,000	180	897	1,077	4·31

Reports of Cases.

PLACENTA ACCRETA WITH COMPLETE INVERSION OF THE UTERUS.

By E. P. HOLLAND, M.B. (Sydney),
Grafton, New South Wales.

Clinical Record.

ON November 1, 1940, I was called to a small nursing home shortly before midnight, to see a patient, E.E.J., who was having a post-partum hæmorrhage. Delivery had been normal and the labour easy. The baby was healthy. I advised the nurse to give "Pituitrin" pending my arrival. She informed me that the placenta was still in the uterus.

On arrival I found the patient, a girl, aged twenty-four years, obviously suffering from the effects of a very severe post-partum hæmorrhage. Bleeding had ceased; and after waiting until one hour from the time of delivery, her condition having improved somewhat, I attempted to express the placenta. The uterus contracted well, and with no undue force the placenta was made to present at the vulva; but immediately it was obvious that it was still attached to the uterine wall, and that a complete inversion of the uterus had occurred. The patient now naturally showed further signs of shock.

No facilities were available at the place of confinement, and the night was warm; I therefore had her removed by ambulance a very short distance to the local hospital. On her arrival there my partner, Dr. N. St. C. Mulhearn, forthwith began to administer saline solution by the continuous intravenous drip method, and all other measures were taken to combat shock. The placenta and uterus were in the meantime wrapped in sterile towels wrung out of saline solution. There was no satisfactory response and the patient died shortly afterwards.

The intention was to treat the shock and hæmorrhage, to give a blood transfusion and to deal with the inverted uterus when the patient's condition justified the attempt.

Post mortem I attempted to strip the placenta from the uterus; but for the most part this was impossible, as it was practically an integral part of that organ. Considerable force was necessary and there was no line of cleavage as in ordinary adherent placenta; after separation the uterine wall was exposed quite deeply in parts.

Discussion.

The condition was one of *placenta accreta*, which occurs, according to Eden and Holland, once in 6,000 to once in 40,000 cases; the incidence of complete inversion of the uterus is given as one in 180,000 to one in 200,000 cases.

It would appear that the treatment of election would have been to give saline solution intravenously followed by a blood transfusion, to make no attempt to express the placenta, and later, if the patient's condition improved, to perform a hysterectomy.

In this regard I would point out, first, that the condition of the patient when I saw her and before any attempt was made to express the placenta, was critical; secondly, that the diagnosis between adherent placenta and *placenta accreta* is apparently possible only when manual removal is attempted in the usual way—a proceeding which, in this case, would, I think, have certainly resulted in severe damage to the uterus, with possible perforation, associated with further shock and hæmorrhage; the result would have been fatal.

I report the case for its rarity and for the difficulty of diagnosis, and therefore of appropriate treatment, even if the condition was suspected, which it was not in this case. The patient was a single girl, from another district, and I have no knowledge of her previous history.

Eden and Holland state that the ætiology is unknown and that the condition results from entire, or almost entire, absence of the *decidua basalis*, in consequence of which the uterine muscle is exposed to invasion by the trophoblast and to penetration by the chorionic villi. The union between the placenta and uterine wall is very intimate; it thus differs radically from simple adhesion of the placenta.

Reviews.

PROGRESS IN ENDOCRINOLOGY.

THE fourth edition of "Recent Advances in Endocrinology" more than maintains the standard set by its predecessors.[1] The writing of this book must have presented many difficulties. In the first place the author had to compress the treatment of a really big subject into the handy form it now takes; further, he had to avoid prolixity and yet retain clarity and fairness when dealing with topics under dispute; and lastly, there must have been a strong temptation, when proofs were being read, to keep on adding the results of the latest research. Admirable judgement is displayed throughout the work. There is a form of scholarship not at all helpful to the reader which is too often found in American publications: it is the scholarship of the librarian rather than the judicial summing up of a critical and competent expert; this book is completely free from this fault. Dr. Cameron is a biochemist and not a clinician, but, though the bedside practice of endocrinology is not emphasized, what he gives must be the foundation of all therapeutic employment of hormones and gland extracts. A wise restraint is everywhere observable—"these views await acceptance", "these observations have not been confirmed", "Fluhmann has discussed the subject in the conservative manner that it needs". As instances of the author's handling of matters still *sub judice* and problems still unsolved, his account of the gaps in our knowledge of thyreoid function may be instanced:

> We know very little of the form of organic combination of iodine in animal food, and still less of that in plant food. We know very little of the mechanisms by which thyroid tissue forms the thyroxine radical, and can only shrewdly guess at the processes of storage and of secretion, and we are still uncertain as to the precise nature of the hormone. We do not know the precise nature of Graves' disease, nor the cause of the beneficial action of iodine (in various forms of combination) in pre-operative treatment. We do not know the initial factors which lead to manifestation of hyperthyroidism in any form. And until these are determined we shall probably not be in a position to find some rational medical therapy.

Another instance is his verdict on the pituitary. As he points out, some fifteen hormones have been described as emanating from the anterior pituitary and nine from the posterior. Collip in 1936 subjected this tendency to father trophic agents on the pituitary to some merciless criticism, and declared that the anterior pituitary produces three only. Dr. Cameron gives the posterior pituitary two and the anterior five, with a possible but unproved sixth, the growth factor.

Some overlapping with other books in this series has been inevitable, but the reader will be glad to have Dr. Cameron's sound judgement and good scholarship on the topics doubly dealt with. There are a very few printer's slips, and these not disturbing; for instance, Heape is spelled Heaps on page 252 and again on page 256, and the name does not appear in the bibliography attached to the chapter. Apart from this trifle the bibliographies are admirable. The illustrations, like others in this series, are on the dark side and lack definition, but war conditions may be responsible. The book is to be warmly commended.

[1] "Recent Advances in Endocrinology", by A. T. Cameron, M.A., D.Sc., F.I.C., F.R.S.C.; Fourth Edition; 1940. London: J. and A. Churchill Limited. Demy 8vo, pp. 440, with illustrations. Price: 18s. net.

DISEASES OF THE NERVOUS SYSTEM.

"DISEASES of the Nervous System", by F. M. R. Walshe, is a splendid book.[1] It supplies the student and general practitioner with the long-felt need for a simplified approach to the subject of neurology.

Walshe, recognizing that in the past the student and general practitioner have so often adopted a defeatist attitude towards the supposed intricacies of neurology, and realizing that this attitude is largely due to false ideas and assumptions based on bad teaching and poorly written books on the subject, has set out to debunk neurology and help the student to an easy understanding of what is perhaps one of the simplest subjects in medicine.

The difficulties of the approach to neurology have been that a detailed and accurate anatomical and physiological knowledge of the central nervous system was a necessary preface to the approach to an endless series of quite unrelated diseases, described in a detached fashion in terms of long strings of signs and syndromes which the student found impossible to learn in any other than parrot fashion.

As described in the preface, the book is planned in two sections. In the first is attempted a general statement of the principles of neurological diagnosis with summary descriptions of the characteristic symptom complexes of disease of the nervous system. In the second half are given accounts of the commoner nervous diseases.

Walshe has set out to write a simple book and has had the courage to keep it simple and to risk the criticism of paying too little attention to detail.

At the end of the book is a small section on the neuroses, tics, habit spasm *et cetera*. We cannot altogether agree with some of the opinions expressed in this section, particularly in regard to ætiology and treatment. However, the author admits in his preface the inadequacy of his treatment of this section and that his main concern is with diagnosis.

[1] "Diseases of the Nervous System Described for Practitioners and Students", by F. M. R. Walshe, O.B.E., M.D., D.Sc., F.R.C.P.; 1940. Edinburgh: E. and S. Livingstone. Demy 8vo, pp. 301. Price: 12s. 6d. net.

The Medical Journal of Australia

SATURDAY, MARCH 1, 1941.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

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THE NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL.

In another place in this issue will be found a report of the meeting of the National Health and Medical Research Council that was held at Canberra on November 6 and 7, 1940. On previous occasions we have had to rely on the official report of the proceedings for any account of the meetings of this body. The statement published in this issue has been received from the Chairman of the council, Dr. J. H. L. Cumpston, Director-General of Health, Commonwealth Department of Health, who writes that it was prepared for this journal by "one of the members of the council". To Dr. Cumpston and the member responsible for the report we offer sincere thanks, for we hold that the practising members of the medical profession should be as conversant as possible with the matters discussed by the council and with the views of its members concerning them. This is the more important because of the comprehensive objects of the council, which, as the Chairman has stated, are concerned with the practical application to the social body of the facts and principles of public health and of medicine and surgery, as well as with the prosecution of research, research being "a search for new facts and principles".

Several of the subjects for which research grants were given call for special comment. In the first place universal satisfaction will be expressed at the determination to continue with the investigation of the health of a group of school children in the Adelaide hills. This is an investigation that is likely to yield important results, and it is being carried on by the willing cooperation of the medical practitioners in the district concerned. The council is anxious that this investigation shall continue and, if the routine examination of the school children is interrupted by the enlistment of any of the medical practitioners concerned, will be prepared to approve the appointment of a full-time medical officer to complete the survey. At the present time the council is making grants in connexion with this investigation towards the salary of a nurse-secretary and a stenographer and towards travelling expenses, a motor car, the purchase of equipment, the upkeep of an X-ray machine, and so on. Members of the community generally will welcome the news that the council is determined to "do everything in its power to assist or subsidize research in any medical problem relating to aviation". With Air-Commodore Hurley in the medical control of the Royal Australian Air Force, we may expect important questions to be investigated and at the same time we have no doubt that this decision of the council will be welcomed by the medical heads of the Royal Air Force in England, who must have many problems that await elucidation. The problems of the Royal Air Force are those of the Royal Australian Air Force, and it is to be hoped that any Australian research in aviation problems will be undertaken only after consultation with the Home authorities, so that there shall be no overlapping. We can well imagine that when the Old Country is faced with constant attack from the air and threat of invasion, it may be ready to delegate to one of the Dominions the investigation of some aviation problem. If Empire resources of men and material are to be pooled, the same should apply to the investigation of medical problems connected with the several services. Of special interest to anyone associated with medical journals is the decision of the council for the first time to subsidize the publication of the results of research. We have always held that when difficulty is experienced in the publication of the findings of research workers, it is the function of bodies such as the National Health and Medical Research Council to assist journals and authors to meet the high cost of publication. Clearly research is sterile unless workers everywhere know what is being and has been done in various fields of endeavour. Confirmation of research work is often necessary, but it is quite obvious that work will be made easier if it is known that others have investigated a particular field and obtained certain results, and duplication may be unnecessary. We therefore welcome the news that at the recent meeting it was resolved to make a grant to *The Australian Journal of Experimental Biology and Medical Science* for the year 1941 of twenty-five shillings a page up to a maximum of £50 "for the publication of work assisted by grants from the National Health and Medical Research Council". This action will be applauded by research workers in all parts of the Commonwealth. At the same time many will hold that it would have been more in keeping with the true scientific spirit if the grant to *The Australian Journal of Experimental Biology and Medical Science* had been made in respect of research work from any source. That the Federal Executive of the Flour Millers' Association has offered the sum of £600 to finance further research into the vitamin *B* content of Australian flour is of great interest, particularly in view of the work by Harriette Chick mentioned in this journal in the issue of January 25, 1941. Those interested in nutrition will also agree with the view that the addition of synthetic vitamin *B* alone to white flour is wrong in principle. The report published in this issue makes unnecessary any long reference to the discussion of the council on the subject of venereal

diseases. It is noted that information on the incidence and methods of control of venereal diseases in the Navy, Army and Air Force is to be obtained from these services and circulated among the States. In this connexion we recall the statement by the officers of the Hospital Ship *Manunda*, whose report was recently published in this journal, that the incidence of venereal diseases among those returned on the ship was almost negligible. This must be in some measure due to the prophylaxis advocated in army circles, and there is no doubt that the introduction of similar measures in civil life would reduce infection. That New South Wales is at a disadvantage in the control of venereal disease in comparison with other States is surely an indication for action, and it is surprising that the council did not take some steps to recommend action to the New South Wales Government, especially as venereal disease was one of the main subjects for discussion at the recent meeting. Among the other subjects discussed at this meeting was cerebro-spinal meningitis. The report on the condition, which was presented by Lieutenant-Colonel M. J. Holmes, will be published in a subsequent issue.

That the National Health and Medical Research Council is doing what it can to fulfil its destiny is clear from the official report and from the document forwarded by the Chairman. In a future report we should welcome a statement of the full amount that is being expended on research. Any sum that is spent in this way will be returned a hundredfold in the days to come.

Current Comment.

MENINGITIS CAUSED BY COLIFORM ORGANISMS.

MENINGITIS caused by the coliform organisms is by no means a common disease, but when it occurs it has certain features that make it a distinctive and particularly interesting problem. For that reason we draw attention to a recent report by S. Rauch and N. Krinsky of a child who recovered from the disease.[1] The report is followed by a survey of the relative literature. The patient was a child, aged twenty days, who became ill with diarrhœa, vomiting and fever. Lumbar puncture revealed a turbid fluid which contained no sugar but pus cells, and had an inordinately high total protein content. The causal organism was described as a "usually non-pathogenic inhabitant of the alimentary tract of the *Bacillus coli anaerogenes* group". Sulphapyridine was administered in the dosage of 0·8 gramme daily in six doses (approximately 1·8 grains per pound of body weight per day). After five days this dose was halved, and after fourteen days administration was stopped. Two days later the temperature rose, and the cerebro-spinal fluid contained pus cells and organisms. Sulphapyridine was again given and in a few days the temperature had fallen and the cerebro-spinal fluid was normal in respect of cell and sugar content. The child was discharged from hospital, but after three days at home relapsed with diarrhœa and fever. The anterior fontanelle was now bulging and examination of the spinal fluid revealed a moderate pleocytosis. Sulphapyridine and two transfusions were given and the child's condition improved, but after some days it had convulsions and manifested palsy of the eye and face muscles. The spinal fluid was again abnormal, the total protein reaching the peak figure of 648 milligrammes *per centum*. Three days later pneumoencephalography and electroencephalography were done; the former suggested considerable atrophy of the left cerebral cortex and the latter abnormal potentials. The child, however, had no more convulsions and did not develop hydrocephalus, but was discharged from hospital apparently well. Nine months later there was no evidence of cerebral abnormality, the child indeed appearing rather more intelligent than is usual at the age. One feature of particular interest is that during the illness the organism causing the meningitis was also found in the blood stream and in the urine.

In the review of the literature that follows this report Rauch and Krinsky point out that though the organisms of the coliform group are an uncommon cause of purulent meningitis, they are a relatively common cause of the disease when it occurs in the newborn. Meningitis is not common in this age group, and reports by various workers show that the coliform organisms cause from 30% to 50% of the infections that do occur. In adults, however, the disease is almost unknown. The outcome of the disease has in the past been almost always fatal, but since sulphapyridine has been used a few recoveries have been reported. In the past hydrocephalus or pyocephalus was a frequent occurrence and often the cause of death. It seems that the likelihood of the development of this sequel is greater in coliform meningitis than in that caused by other organisms. Another feature of the case reported, and a feature that we have seen in these cases, is the very great increase in the protein content of the cerebro-spinal fluid. The pathogenesis of the disease affords an opportunity for interesting observation and speculation. In many of the cases reported in the literature the authors have described a primary focus from which the causal organism was isolated and from which they presumed it spread to the meninges. The foci mentioned are the urinary tract, the bowel, the skin, the mouth, the ear and the umbilicus. In the present case both the urine and the blood stream were infected. Throughout life the coliform organisms are normally found in the bowel and are frequently the cause of urinary tract inflammation. The generalized infection and spread to the meninges in new-born babies is probably bound up with the notoriously poor formation of antibodies by these young children. Contact with these organisms is common even in the first few weeks of life and the baby, having a poor barrier against them, becomes infected. At autopsy this generalized infection has frequently been noted.

Another important feature of the case upon which these authors lay some stress is the difficulty in the diagnosis of meningitis in a young baby. The classical signs of neck rigidity and Kernig's sign are usually absent. Fever which cannot be explained on other grounds, irritability, hyperæsthesia, incoordination of the eye muscles, and convulsions are suggestive. In their presence a lumbar puncture should be done and establishes the diagnosis. The treatment that has been used in the past consists of the administration of vaccine, human serum and parental blood, and the results have been uniformly bad. Several recoveries have now been recorded with the use of sulphapyridine and blood transfusions. The disease still tends to be rather long and relapses are likely to occur. Hydrocephalus is still likely to develop and death is not infrequent. The ultimate outcome in this or any other child, of course, cannot be accurately estimated until five or six years have passed. The findings on encephalography indicated severe cerebral damage, and this is consistent with autopsy findings as seen by anyone who deals with these cases. It is surprising indeed that the child appears to have made so good a recovery.

This is a valuable report of a characteristic disease of the neo-natal period. Though recovery occurred we would still emphasize the gravity of this disease, and the tendency for chronic sequelæ to develop. We would emphasize, too, the difficulty of the diagnosis of meningitis in young babies. Any obscure pyrexial disease of this period is an indication for lumbar puncture. Now that

[1] *American Journal of Diseases of Children*, December, 1940.

the use of sulphapyridine has given some hope of recovery, it is a grave error not to make the diagnosis and a still graver error not to treat the child even without a diagnosis. The best treatment seems to be the vigorous administration of sulphapyridine which these little babies tolerate remarkably well. Blood transfusions may have some immunological value, though the amount of antibody reaching the cerebro-spinal fluid is certainly small. They unquestionably have an effect in stimulating hæmopoiesis in a child which has become severely anæmic from chemotherapy. There is no doubt that they are a most useful adjunct to the treatment of meningitis by drugs of the sulphonamide group.

Another feature of this case report and of so many reports that are appearing now is the relapse after the sulphapyridine has been suspended. Meningitis is an exceedingly grave disease and in most cases hope of recovery rests almost solely on this drug. It is known from experimental and clinical experience that some organisms, particularly the pneumococcus, having been subjected to a sublethal dose of the drug and having survived, then show a tolerance for the drug which they previously lacked. It is of the utmost importance therefore that the administration of the drug in any case of purulent meningitis should not be discontinued until all possible measures have been taken to ensure that the cerebro-spinal fluid is free from organisms. Meningococcal meningitis is the only type of the disease in which any laxity can be tolerated, and even there it is unwise. It is a safe rule that the drug should not be suspended until the patient is apyrexial and clinically well, and until a lumbar puncture has yielded fluid from which organisms cannot be cultured by careful and correct laboratory methods.

THE DEVELOPMENT OF COLLATERAL CIRCULATION.

ANYTHING that Thomas Lewis writes on the cardiovascular system deserves close attention. He has recently described three exceedingly interesting patients with long-standing arterio-venous fistulæ and has made some observations that are of importance to our understanding of the mechanism that causes collateral circulation to develop when arterial channels are injured.[1] When, as the result of a perforating wound, the lumina of the main artery and vein of a limb become freely united, an immediate and striking change comes over the whole circulation. Throughout the whole body the pulse assumes a characteristic collapsing quality; because the blood escapes rapidly from the artery through the arterio-venous fistula and not slowly through the capillaries, the diastolic pressure cannot be maintained. The pulse therefore collapses rapidly and rises again rapidly during systole. In the limb itself circulation is still more disordered. The blood flow to the distal part is diminished for the following reasons. In the first place much of the blood destined for the limb is short-circuited through the fistula to the vein. As a result the intravenous pressure rises and the return of blood from the distal veins in the limb is hampered. This in turn further decreases the arterial blood flow past the fistula. In the course of time, however, this reduction of blood flow to the damaged limb becomes counteracted. Lewis makes this special point in describing his three patients.

In all three patients the original injury had been a bullet or shrapnel wound producing a large arterio-venous leak, situated high in the thigh in two cases and in the region of the knee joint in the other. The examinations which Lewis records with such interest were made some twenty years after the original injuries. The striking fact revealed in all three was that there was ample evidence of a blood supply to the damaged limb, not equal to, but greater than to the normal limb. A number of observations indicated this greater flow to the limb distal to the fistula. In all three patients the pulses were larger in this part of the limb than in the normal one, whether measured by digital or instrumental means. The veins too were larger and in two patients frankly varicose. The temperature in the damaged limb was in all cases higher than in the sound one. In two patients the heat loss, accurately measured, was found to be considerably greater from the damaged limbs. These were congested and a little enlarged. That this enlargement was not due to congestion of stagnant but of actually circulating blood is amply demonstrated by the observations of pulsation, temperature and heat loss. Nor was the increased circulation due to the development of collateral arterial channels, none of which could be found by careful palpation. The clinical findings indicated rather an enlargement of and increased blood flow in the main artery distal to the fistula. Such an enlargement has been described at autopsy by Breschet in yet another case.

The attempt to explain the hypertrophy of the artery distal to the fistula, Lewis points out, raises the whole question of the mechanism that produces collateral circulation in any part of the body. It has been generally accepted that if an artery is obstructed the pressure in the vessel becomes increased proximal to the obstruction and decreased distal to it, and the blood flow from the proximal branches increases. Gradually these branches hypertrophy and an adequate collateral circulation is established. Such observations led to the theory that the growth or shrinkage of arteries is controlled by the amount of blood flowing through them. Such a theory would explain the collateral circulation developing from an obstructed artery or the increase in size of the artery leading to an arterio-venous fistula. It cannot, however, explain the increase in size of an artery distal to such a fistula, "for the fall in arterial and rise in venous pressure, which are the necessary consequences of the original lesion, must tend primarily to retard rather than to increase the blood flow in these channels". Lewis suggests that the growth of arterial channels to any region depends on a chemical substance produced in the tissues of the region as a result of insufficient blood flow. Such a substance produced by the need of the tissues affords a stimulus adequate to make good that need. This hypothesis affords an explanation of the phenomena recorded in these important cases. It may sound speculative, but it is sound speculation.

[1] *Clinical Science*, October 30, 1940.

BRONZED DIABETES IN A WOMAN.

HÆMOCHROMATOSIS or bronzed diabetes is an uncommon disease in men but is extremely rare in women. Sheldon, in a review of literature published in 1934, records 295 cases in males but only 16 in females, a sex ratio of about 18 to 1. R. D. Lawrence[1] states that he has seen and treated 28 proved cases of this disease in men during the past sixteen years, but has only now for the first time treated a woman with hæmochromatosis. The patient, a woman, seventy-three years of age, was referred to his diabetic clinic with diabetic symptoms and heavy glycosuria. She was a brunette, but had noticed that her colour had been becoming darker for many years. The whole skin was a dirty light brown colour, but the exposed area—the hands and especially the face—were of a darker slaty brown colour typical of hæmochromatosis. The liver was enlarged, very firm, fairly smooth and slightly tender. The diabetes was moderately severe. "A skin biopsy was carried out on the left forearm. . . . The usual staining methods and chemical tests demonstrated an increased deposition of melanin in the basal layer of the epidermis, and, more important, an iron-bearing pigment in the basal layers of the sweat glands, ducts and sebaceous glands. This deposit was nowhere heavy and always patchy, but proved the condition beyond doubt." So far the preponderantly male incidence of hæmochromatosis has not provided a clue to the cause of this curious error of metabolism, though most clinicians would expect it to do so.

[1] *The Lancet*, October 19, 1940.

Abstracts from Medical Literature.

PHYSIOLOGY.

Dark Adaptation and Experimental Human Vitamin A Deficiency.

S. HECHT AND J. MANDELBAUM (*The American Journal of Physiology*, October, 1940) show that it is possible to demonstrate vitamin *A* deficiency in a diet by its effect on the dark adaptation of the subject. They report the result of an investigation. The retinal location, the colour and size of the area tested, and the duration and extent of the preceding light adaptation were kept constant according to the standard procedure recommended by Hecht and Schlaer. A diet calculated to yield about 150 international units of vitamin *A* per day was taken by 17 subjects, 14 of whom showed an immediate rise in their visual threshold, which continued to rise as the diet was prolonged. The authors think that failure of the other three subjects to respond for as long as three months may have been due to an exceptional storage of vitamin *A* in the tissues, although their ultimate rapid response indicated rapid storage depletion. The cone thresholds rose less than the rod thresholds, and their behaviour was approximately parallel. The best single criterion of these changes is the final rod threshold after thirty minutes in the dark. None of the subjects showed any skin symptoms, and only the two most extremely affected individuals recorded a subjective awareness of their raised visual thresholds. Partial recovery of the visual threshold was accomplished in some individuals by a single large dose of vitamin *A*, but the extent of this recovery was variable. Such recoveries were never complete and were always temporary. Permanent recovery from the effects of the deficient diet was slow, requiring months. The fastest subject returned to normal in six weeks, the slowest still had a high threshold after three months, but had recovered completely after one year. Efforts to influence the visual responses during and after the taking of the diet deficient in vitamin *A* by the ingestion of other vitamins yielded only negative results.

Measurement of Venous Pressure in Man.

J. P. HOLT (*The American Journal of Physiology*, October, 1940) describes a method for the measurement of venous pressure in man that eliminates the hydrostatic factor. The author criticizes the reference points suggested by Moritz and Tabora and of Eyster as being placed too far ventrally, but finds results in agreement with those of Recklinghausen and Lyons. The pressure in the antecubital vein is measured by a modification of the direct method of Moritz and Tabora, physiological saline solution being used in the manometer system in place of citrate solution. The pressure is determined firstly with the subject supine, the arm lying well below the centre of the body and abducted to about 45°, and then with the subject turned over into the prone position with the arm well below the centre of the body and abducted to about 45°. All pressures are referred to the level of the spine as zero. The mean of the two pressures equals the venous pressure, and the reference point is located at the point in the chest midway between the top of the two columns of saline solution in the two pressure measurements. Venous pressure determined in this manner varied between 7·8 and 14·1 centimetres of physiological saline solution, 80% of the subjects presenting variations between 7·8 and 12·1.

The Role of Dicarboxylic Acids in Blood Coagulation.

G. J. MARTIN (*The American Journal of Physiology*, September, 1940) describes the findings of earlier workers concerning the effect of various dicarboxylic acids and some other substances on the coagulation time of blood. Figures are then given, which show the effect of these dicarboxylic acids on the coagulation time of the blood from chickens suffering from vitamin *K* deficiency. The clotting time was restored to normal in every case, even though the site of injection was varied. The time for the production of the maximum effect on the coagulation time varied from thirty minutes to seven hours, whereas in the normal animal the maximum is reached between thirty minutes and one hour. A table is given showing the effect on the coagulation time of the normal rabbits of the injection of various substances, including many dicarboxylic acids. The activity of the dicarboxylic acids in this respect decreases as the number of carbon atoms increases, malonic acid, because of its greater solubility and lesser toxicity, being preferred in therapeutics. To explain the mechanism underlying further results, the author suggests the existence of a calcium prothrombin. The addition of a little oxalate to blood decreases the time of clotting because some calcium is taken from the complex by the oxalate and the amount of free prothrombin is increased. This is then available for conversion into thrombin, there being still sufficient calcium ions to act as a catalyser, and coagulation is thus speeded up. The addition of large amounts of oxalate increases the prothrombin, but the remaining calcium ions are not sufficient for the catalytic action and coagulation is inhibited. Again, the effect of excess calcium ion on the blood is to inhibit coagulation because the amount of prothrombin present is so diminished by being converted into calcium prothrombin that there is not sufficient left free for conversion into thrombin, and so clotting is delayed. Further support is also supplied by the fact that dicarboxylic acids have no effect on the coagulation time of heparinized blood, it being generally accepted that heparin exerts an antithrombase action in the second part of the coagulation.

The Prolonged Action of Acidified Solution of Protamine Zinc Insulin.

MELVILLE SAHYUN (*The American Journal of Physiology*, September, 1940) describes the preparation of a clear acidified solution of protamine zinc insulin containing five milligrammes of zinc per 100 units. Subcutaneous injection of this preparation into fasting rabbits causes a prolonged hypoglycæmia greater than that which follows the injection of a similar amount of crystalline insulin with or without added zinc. In an earlier paper the author claims to have demonstrated that when an acidified solution of insulin is subcutaneously injected, the hydrogen ion concentration of the injected material must reach equilibrium with the tissue fluid before absorption can take place. Directions for the preparation of the solution of protamine zinc insulin are given. Unlike the preparation of precipitated protamine zinc insulin usually marketed, this solution is clear. The effects of ageing are described. Samples were incubated at 52° C. for nine days with little loss in potency. The author mentions that injection of two units causes a greater prolongation of hypoglycæmia in rabbits when the material is concentrated (forty units per millilitre) than when it is more dilute (five units per millilitre). Comparative graphs are given showing the average prolongation of hypoglycæmia in groups of 20 rabbits injected with crystalline insulin, protamine zinc insulin pH 7·2 (marketed product) and clear solution of protamine zinc insulin. Apart from the prolongation of hypoglycæmia following injection of the clear solution, the onset of its action compared with that caused by the pre-precipitated protamine zinc insulin, is very rapid. This is clinically desirable, as it would no longer be necessary to administer an adjunct dose of a fast-acting insulin to maintain the blood sugar level for the first few hours following the injection of protamine zinc insulin (pH 7·2) into a diabetic patient.

Intralumen Pressures of the Digestive Tract.

D. A. BRODY, J. M. WERLE, I. MESCHAN AND J. P. QUIGLEY (*The American Journal of Physiology*, October, 1940) discuss critically the measurement of the intralumen pressures of the digestive tract, especially of the pyloric region. The ordinary balloon-water manometer method for the registration of gastro-intestinal pressures is inadequate. Many objections are related to the high volume-pressure ratio, but in addition the recorded pressures will vary with the size, shape and volume of the balloon. Pressures can be accurately measured from an open tip in the gut with an optical manometer for registration. The basal pressure of the pyloric antrum usually exceeds the basal pressure in the duodenal bulb, and both rise moderately when food enters the stomach. Subatmospheric pressures are common in both regions. Periodically, phasic pressure changes amounting to that of about 30 centimetres of water develop in both regions. The phasic pressure changes of the bulb are generally closely related to those in the antrum. They are produced respectively by bulbar or antral contractions. The swallowing or smelling of food produces a transient inhibition of these pressure changes even in animals whose vagus has been cut. After feeding this inhibition is quickly supplanted by phasic changes more uniform, more persistent and frequently of greater magnitude than those preceding the feeding.

BIOLOGICAL CHEMISTRY.

Physiological Hypertrophy of the Parathyreoids.

A. W. HAM, N. LITTNER, T. G. H. DRAKE, E. C. ROBERTSON AND F. F. TISDALL (*The American Journal of Pathology*, May, 1940), in studies on rats, have shown that physiological hypertrophy of the parathyreoid glands is caused by hypocalcæmia and not hyperphosphatæmia. Parathyreoid

hypertrophy was not necessarily associated with rickets; it occurred only in "low calcium" rickets and not in "low phosphorus" rickets. Under a dietary régime which produced a low blood calcium level with a normal phosphate level, parathyreoid hypertrophy developed; but it did not develop when the blood phosphate level was raised and the blood calcium was kept at a normal level.

Vitamin C and Tyrosine Metabolism.

R. R. SEALOCK AND H. E. SILBERSTEIN (*The Journal of Biological Chemistry*, August, 1940) have demonstrated, by experiments with guinea-pigs, that vitamin *C* is essential for the normal metabolism of the amino-acids tyrosine and phenylalanine. The feeding of tyrosine to guinea-pigs on a diet deficient in vitamin *C* resulted in the excretion of homogentisic, p-hydroxyphenylpyruvic and p-hydroxyphenyllactic acids. Administration of l-ascorbic acid in amounts of ten milligrammes or less completely prevented the excretion of these metabolites. The specificity of the ascorbic acid action was demonstrated by the fact that ten milligrammes of d-isoascorbic acid were ineffective in replacing a similar weight of l-ascorbic acid, but 200 milligrammes of the former, an amount equivalent to the natural vitamin in antiscorbutic activity, were able to prevent the metabolite excretion. The efficacy of single doses of ascorbic acid was found to depend on the state of vitamin *C* saturation of the tissues.

Metabolism of Sodium.

D. M. GREENBERG, W. W. CAMPBELL AND M. MURAYAMA (*The Journal of Biological Chemistry*, October, 1940) have studied, by means of the radio-active sodium isotope Na^{24}, the absorption of sodium from the gastro-intestinal tract, the rate of secretion in the urine and the distribution in certain viscera. Rats were used for the experiments. The absorption of sodium was extremely rapid; within ten minutes about 75% of the administered sodium chloride had been absorbed from the stomach and small intestine, and within an hour about 95%. The course of excretion of labelled sodium through the kidney followed an exponential curve, in contrast with potassium, which had been found to follow a linear course. The absorbed sodium was very rapidly distributed throughout the body fluids and tissues, so that a maximum of specific accumulation was reached in most cases in about ten minutes; the specific accumulation then persisted for many hours at a constant level. The evidence available indicated that the labelled sodium rapidly permeated to all regions of the body where sodium was normally present.

Nicotinic Acid.

D. MELNICK, W. D. ROBINSON AND H. FIELD, JUNIOR (*The Journal of Biological Chemistry*, October, 1940), have reported in three papers studies on urinary pyridine compounds, the urinary excretion of nicotinic acid and its derivatives by normal persons and the factors influencing the concentration and distribution of nicotinic acid in the blood. Nicotinamide was stable in blood stored at 5° to 8° C. for at least five days. The values for nicotinic acid in the blood of normal males averaged 0·69 milligramme *per centum*, and in females 0·62 milligramme *per centum*. Approximately 90% of the total nicotinic acid of the blood was in the corpuscles. In anæmic blood samples the corpuscular nicotinic acid concentration was sufficiently high for the whole blood values to remain in the normal range. A recently ingested meal, coffee drinking, and smoking did not affect appreciably the blood nicotinic acid values. When an oral test dose of nicotinic acid was taken by the fasting subject, there was a prompt increase in the blood values followed by a rapid return to values somewhat above the basal level. When an oral test dose was taken after eating, there was a slow increase in the nicotinic acid of the blood. The plasma (free nicotinic acid) values and not the whole blood figures coincided with both the extent of the urinary secretion and the severity of the unpleasant side reactions associated with the taking of nicotinic acid. When a normal subject received repeated doses of the compound, the elevated blood levels persisted long after dosage ceased. There was a similarity in blood levels after nicotinic acid and nicotinamide ingestion; this was in marked contrast with the much lower urinary excretion following administration of the latter.

Estimation of Sulphanilamide, Sulphapyridine and Sulphathiazole.

M. BODANSKY (*American Journal of Clinical Pathology*, November, 1940) has described details of analytical procedures based on the method of Bratton and Marshall for the estimation of sulphanilamide, sulphapyridine and sulphathiazole in blood. The same procedures are used in the estimation of all three drugs. Total sulphanilamide in blood includes, besides the "free" drug, the acetyl derivative formed as a detoxication product, and this can be determined after acid hydrolysis. Full details of the methods are given. By slight modifications of the procedures used for blood, analyses may be made of urine, cerebro-spinal fluid and other body fluids.

C. E. LANKFORD (*ibidem*) has worked out a series of conversion factors, by the use of which the concentration of any one sulphanilamide derivative can be determined with the use of a standard of any other similar compound. The figures are given for sulphanilamide, sulphapyridine, sulphathiazole, sulphanilyl-sulphanilamide and sulphamethylthiazole. With the exception of the sulphanilamide:sulphanilyl-sulphanilamide ratio, the experimental values closely approximate the theoretical values. Although the colour values of the various sulphanilamide derivatives are not identical, the differences are not enough to constitute an objection to the use of conversion factors for routine clinical laboratory work.

Albuminuria and Hypertension.

M. BRUCER AND S. C. ROBINSON (*American Journal of Clinical Pathology*, November, 1940), in a study of 2,009 men and 500 women, found that albuminuria occurred far more frequently among persons with hypertension than among those with normal blood pressure. One-fourth of the hypertensive groups showed albuminuria compared with 8% in the low pressure groups. This high incidence of albuminuria was considered an underestimate of the actual incidence in hypertensives, because the study was based on a single examination of the urine of each subject, whereas albuminuria is frequently an intermittent finding, especially in early renal impairment in the adult. The authors conclude that the evidence supports the view that hypertension is not a benign disease and that albuminuria is an early sign of renal impairment. Data are also presented on the association of albuminuria with age, weight, build, height, surface area, mean blood pressure and pulse pressure.

Vitamin K in Hæmorrhagic Diseases of Children.

I. NEWTON KUGELMASS (*American Journal of Clinical Pathology*, October, 1940) has prepared prothrombin from human blood plasma. The product showed properties similar to those observed for animal prothrombin. The blood of infants was found to be undersaturated with prothrombin until the blood volume reached about one litre, and up to this time the concentration of prothrombin could be increased by vitamin *K* administration. When the child's blood reached the adult level of prothrombin concentration, vitamin *K* administration was without effect. A diet adequate in milk and leafy vegetables was considered to supply ample amounts of the vitamin. Prothrombin deficiency in the blood clotting mechanism was not a determining factor in hæmorrhagic diseases of infancy and childhood, except in the relatively rare latent or manifest hæmorrhagic diseases of the new-born, *pseudohæmophilia hepatica*, *icterus gravis neonatorum* and occasionally in hereditary pseudohæmophilia. Vitamin *K* therapy was effective for the two former diseases and possibly also for the two latter.

Chemical Determination of Vitamin C Deficiency.

G. J. KASTLIN, C. G. KING, C. R. SCHLESINGER AND J. W. MITCHELL (*American Journal of Clinical Pathology*, December, 1940) have described in detail methods for the chemical determination of vitamin *C* in blood plasma and urine. The limitations of single fasting blood determinations as a measure of vitamin *C* nutrition are discussed and a clinical method for evaluation of the state of nutrition is described. This is based upon the determination of the fasting blood plasma level and urinary excretion, followed by intravenous injection of 500 milligrammes of ascorbic acid, and subsequent determination of the blood plasma level after five minutes and both blood plasma and urinary excretion values after one, two, three and four hours. The typical normal saturation curve has the following characteristics. The fasting blood level is 0·7 milligramme *per centum* of ascorbic acid or higher; the five-minute blood level is relatively high, ranging from 4·5 to 9·0 milligrammes *per centum*; the rate of return of the blood concentration from the five-minute peak to the four-hour level is gradual, indicating no great avidity of the tissues for vitamin *C*; the four-hour blood level is distinctly above the fasting blood level; urinary excretion of the test dose is greatest in the first hour, and the total urinary excretion in four hours is 40% or more of the test dose. The typical severe deficiency curve shows: the fasting blood level is below 0·4 milligramme *per centum*; there is only a slight variable rise of blood level at five minutes; the blood concentration falls rapidly to near the fasting level; the total urinary excretion ranges from a few milligrammes to 20% of the test dose.

The National Health and Medical Research Council.

THE NINTH SESSION.

THE following account of the ninth session of the National Health and Medical Research Council has been received from the Chairman, Dr. J. H. L. Cumpston, who writes that it was prepared for this journal by one of the members of the council.

The ninth session of the National Health and Medical Research Council[1] met at the Australian Institute of Anatomy, Canberra, on November 6 and 7, 1940. The Minister for Health for the Commonwealth, the Honourable Sir Frederick Stewart, expressing his regret that he was unable to attend the opening session, sent the following message to the council:

> At your meeting this time last year, when we had only just begun to face the reality of war, I urged upon you that it was important for all national reasons that the standard of health of the individual must be maintained at its highest level, and I asked you to give an important place in your discussions to a consideration of any measures that may be possible under existing circumstances, which would have as their object this conservation of national health.
>
> I am well aware and gratefully acknowledge that there has been a ready response by each of you to this request, but perhaps by repetition I can encourage you to continue and expand these efforts, and so I send you again the same message as I sent a year ago.
>
> We are all hoping that it will not be necessary to repeat this message next year, but if it is, we all recognize that with each year the necessity for physical endurance and a high state of physical efficiency becomes increasingly great.

The report of each session of the council follows the items listed on the agenda of the session. It is, however, worthy of note that the field of discussion and of interchange of opinion and experience is far wider than the formal minutes or the report of the session might indicate. In an inaugural address to the first session of the council, the Chairman (Dr. J. H. L. Cumpston) said: "'Public health is merely the application of the facts and principles of medical science to the social organism; medicine and surgery are the application of exactly the same facts and principles to the individual organism; and research is the search for new facts and principles.' The title of this council indicates that its purpose is to combine all these aspects of medicine so that their relation to the social body may be expressed in practical terms and its constitution is such that all agencies engaged in this common campaign are represented."

Against this background of clinical medicine and research during and between sessions there are few subjects which escape attention over the whole range of public health and social medicine, in the widest sense of these terms. Problems of tuberculosis, for instance, do not appear as a separate item on the agenda or in the report of this session. Nonetheless, reference to tuberculosis was made in connexion with five research grants, in relation to public health under war conditions and to physical fitness and nutrition, and as one subject in which public education is achieving results. This reference from so many angles is significant, having regard to the constitution of the council and its special and Commonwealth-wide representation.

In presenting the report of the British Medical Research Council for the year 1938-1939 (published in January, 1940), Earl Stanhope, Lord President of the Privy Council, wrote that:

> As the war proceeds, the Medical Research Council will be required to undertake the investigation of special medical problems as they arise: some of them can be foreseen, and steps which have already been taken to promote new researches are mentioned in the following report.

These words might be quoted as an introduction also to the report of the Australian National Health and Medical Research Council. The following notes summarize features of the report of this recent session of the council, with special reference to matters which have a special importance at this present time.

Medical Research.

In accordance with custom, the reference subcommittee of the council met on the day preceding the opening of the session. Each application for a research grant, or extension or variation of an existing grant, is studied together with the reports of specialist referees on each subject of research. The subcommittee reports in detail to the full session, which formally endorses or refuses each recommendation of this report.

At this session 42 applications for grants were received. Of these, 26 renewals of existing grants and seven new grants were approved and nine applications were refused. Four grants were discontinued with the enlistment for military service of the research worker; in one instance a new grant was approved for a colleague to continue the research work.

For administrative convenience, rather than as a hard and fast grouping of research subjects, current grants are listed under the following headings: bacteriology, biochemistry, dentistry, medical surveys, neurology, nutrition, obstetrics and gynæcology, ophthalmology, physiology and pharmacology, tropical physiology and hygiene, tuberculosis, virus diseases.

These headings indicate the wide field of work now covered. The session reports merely list the items of each individual grant, but details of these grants and of the work being done are recorded in a separate report which is presented to Parliament and published each year in accordance with the provisions of the *Medical Research Endowment Act* of 1937.

Special interest attaches at the present time to research work which has a definite relationship to the war effort. The story is now well known of the development of blood transfusion services and the "blood bank". Much original work has been done in Australia, and the National Health and Medical Research Council has joined with the Australian Red Cross to assist research at the Walter and Eliza Hall Institute, working in collaboration with the Commonwealth Serum Laboratories. Following investigations into changes in blood on storage, comparative tests of the use of whole blood and of serum in transfusion gave encouraging results with serum. Since serum will keep under suitable conditions for prolonged periods, this is a practical advance. Research is now concentrating on satisfactory methods of preparing a dried serum which will be readily transportable and especially convenient for active service conditions.

In the department of physiology in the University of Sydney, work has proceeded under grant on certain respiratory phenomena (especially the so-called "oxygen trough of expiration") and cardiac output. Certain aspects of this original work have opened up new avenues of investigations into basic physiological factors and have led to a promising approach to some of the problems met with in the use of high-speed fighter aircraft.

In the pathological laboratory of the Children's Hospital, Melbourne, work has been done, and is proceeding, to overcome the known limitations of the microscopic search of smears of sputum in the bacteriological diagnosis of pulmonary tuberculosis. The large scale radiological examination of men of the Australian Imperial Force has provided a unique opportunity for correlating radiological with bacteriological findings in this research. The successful use of micro-radiography in the services will lead naturally to its further application to the civil community. It is obvious that radiological surveys will be greatly enhanced if parallel bacteriological findings can also be adduced. This investigation is being followed with considerable interest as a practical advance in the fight against tuberculosis.

In the dental metallographic research laboratory of the University of Melbourne investigations under a research grant are being continued into the properties of dental alloys, gold substitutes, amalgams, cements, waxes, dental plastics and impression compounds. Since the war began, dental supplies are being manufactured in Australia in increasing quantities. The research work of this laboratory has already been of great assistance to Australian manufacturers who are now producing materials equal, and in many respects superior, to those formerly imported from overseas.

Infectious diseases likely to be of epidemic importance under war conditions include some of the virus group. Assistance has been given to the work in this field at the Walter and Eliza Hall Institute, work which is already well known. Grants have also been made to assist the less widely known work which is also being done at the Medical

[1] Dr. J. H. L. Cumpston, C.M.G. (Chairman), Lieutenant-Colonel M. J. Holmes, D.S.O., and Dr. F. McCallum (Commonwealth); Dr. E. S. Morris (New South Wales); Dr. H. N. Featonby (Victoria); Sir Raphael Cilento (Queensland); Dr. E. Angas Johnson (South Australia, *vice* Dr. A. R. Southwood, on military duty); Dr. R. C. E. Atkinson (Western Australia); Dr. the Honourable J. F. Gaha, M.L.C. (Tasmania, *vice* Dr. B. M. Carruthers, on active service); Dr. H. Ritchie (Royal Australasian College of Physicians); Professor H. R. Dew (Royal Australasian College of Surgeons); Professor M. L. Mitchell (Australian universities having medical schools); Dr. J. Newman Morris, C.M.G. (Federal Council of the British Medical Association); Sir Victor Wilson and Mrs. I. H. Moss, C.B.E. (lay representatives appointed by the Commonwealth Government).

and Veterinary Research Institute in Adelaide. With the war there will be an increasing use of the drugs of the sulphanilamide class in the treatment particularly of infected wounds, gonorrhœa and cerebro-spinal meningitis. Investigations to gain further knowledge of the toxic effects of these drugs and of their effect on blood pigment metabolism are being actively pursued under research grants at the Institute of Medical Research at the Royal North Shore Hospital in Sydney.

It is of some significance that these and other items of current research work, whilst orientated to present military needs, have a permanent applicability to civil conditions. Recently Dr. S. F. McDonald pointed out in the Jackson Lecture (THE MEDICAL JOURNAL OF AUSTRALIA, December 7, 1940, page 590) "some debts of medicine to the fighting services". He showed how much of the research of war-time made lasting contributions to medicine, surgery and the public health. The recent Australian research on blood transfusion is an outstanding example, since the advances made, invaluable on active service, will at the same time help to reduce maternal mortality (in cases of post-partum hæmorrhage) and the growing toll from civil accidents.

This recognition of the needs of the civil community against the background of war was a feature of the discussions of this session of the council. Especially was this so with regard to research and movements relating to health and disease in infants and children. Reference is made below to research into problems of nutrition and the physical fitness movement. One research grant in which all members showed special interest, is to further a systematic study of the health of a group of children in the Adelaide hills. The work is being done by local practitioners with secretarial assistance for the collation of records. Special provision was approved to meet difficulties which have arisen with some of these medical men proceeding on military service; the continuity of this promising field investigation is therefore ensured.

An item of research which over some years has been the subject of collaboration with local practitioners and State and Commonwealth laboratories, is the difficult one of differentiating the short-term fevers of North Queensland. An interim report on work under this grant appeared in this journal for November 30, 1940, page 556, reporting the separation of the so-called "coastal fever" from scrub typhus and the isolation of an organism of the anthrax group which appears to be the causal agent of the disease, transmitted by some vector which may be a mite, mosquito or tick.

References to published reports of workers under grants from the council recall that it is a matter of some mutual satisfaction that during the year 1940, 28 articles reporting such work have appeared in THE MEDICAL JOURNAL OF AUSTRALIA. In the more specialized pages of *The Australian Journal of Experimental Biology and Medical Science*, articles reporting work done under grants from the council filled 154 of the 340 pages of the first three numbers for 1940. At this recent session, Professor Mitchell, who is editor of this latter journal, referred to the present difficulties of research workers in securing publication of papers in oversea journals. The council acknowledged the importance of the opportunities afforded by publication in the Australian journals and of the maintenance of critical editorial supervision and of a high standard for acceptance.

Whilst recognizing the essential part which publication must play in any system of research, the council has from the outset rightly refused to assess results of any research work or of its own activities by the girth of volumes of collected papers. Included in the first resolution of the first session of the council, held in Hobart in 1937, the primary objectives of the medical research proposals of the council were defined as:

> (*a*) encouraging young medical graduates to take up medical research as a career; and
>
> (*b*) securing definite and assured continuity and permanence to the research system now being inaugurated.

Allowing for the distractions of war-time, the council felt that the work done during 1940 was satisfactory and that the programme approved for the year 1941 indicates that the system of research endowment organized by the council has achieved no small measure of success within the terms of these original objectives.

Public Health under War Conditions.

At the seventh session of the council (November, 1939) a resolution was adopted and submitted to the Commonwealth Government stressing important aspects of the public health in war-time. The need was urged for full cooperation of military and civil services in the safeguarding of the community against epidemic and venereal diseases. The Government was asked that every consideration should be given to civil requirements of essential drugs and medical equipment, and that health services should be retained with their present standards and full resources. The resolution stated, with emphasis, that our war effort and the national future depended on the maintenance of the health and vigour of children and adolescents and of good working conditions and cultural standards of the whole community.

This recent session reviewed Australian public health as it has been and may be affected by war-time conditions. Steps taken to ensure adequate supplies of drugs and medical equipment were reported (this is adequately recorded in an address by Sir Alan Newton on "Problems Relating to the Supply of Medical Equipment" which appeared in THE MEDICAL JOURNAL OF AUSTRALIA, November 9, 1940, page 453). The council agreed to continue grants for work on the standardization of the active principles of medicinal plants grown in Australia, in cooperation with the Council for Scientific and Industrial Research, at the request of the Medical Equipment Control Committee.

Referring to the earlier resolutions of the council and to this work, Dr. J. F. Gaha questioned whether: "We have provided for essential drugs but not for the doctors to prescribe them." The council discussed at some length the possibilities of a reduced reserve of medical men for the civil population, and of ways and means of providing for any shortage of men in practice. The representatives of the universities and the hospital teaching schools reported on the scheme already prepared by the deans of faculties to provide a shortened medical course should the need arise. Reference was made to the proposal then under discussion in Queensland and New South Wales to amend legislation which requires twelve months' hospital service before admission of graduates to registration. The general feeling of the council was definitely against any measure which would in any way reduce the clinical training and the recognized high standard of the Australian graduate. It was agreed that an apparent shortage of medical men for practices in country districts exists; but it was considered that with the expected quota of graduates from the medical schools, and more flexible adjustment between military and civil needs, the distribution of medical men could be so arranged that civil services and practice would be fully covered. Nonetheless, there was general agreement that the situation must be closely watched, and the council adopted the following resolution:

> This council recommends to the Government through the Minister for Health that the Central Committee for the Coordination of Medical Services take immediately such steps as are necessary to provide for a progressive supply of medical men for civil needs in association with and complementary to military needs.
>
> The council further recommends that each State Coordination Committee be requested to place the position in respect of that State immediately before the Central Committee for the Coordination of Medical Services for appropriate action by that body.

An important and interesting contribution to the deliberations of the council was made by Air-Commodore T. E. V. Hurley, Director-General of Medical Services of the Royal Australian Air Force. He referred to various medical and health problems associated with the development of that service and its relation to the Empire Air Scheme. He asked especially that the council should cooperate and assist in the highly technical problems of research which are being dealt with by the Flying Personnel Research Committee, with special reference to investigations into physiological problems of aviation. A similar body in England, under the chairmanship of Sir Edward Mellanby, of the Medical Research Council, has already done valuable work. The council immediately agreed to accede to Air Commodore Hurley's request and adopted the following resolution:

> The National Health and Medical Research Council assures the Air Board through Air Commodore Hurley that it will do everything in its power to assist or subsidize research in any medical problem relating to aviation.
>
> The council, in view of the possible urgency of problems that may arise and the necessity for secrecy, authorizes the chairman after consultation with the Reference Subcommittee to approve of grants for research by the Flying Personnel Research Committee.

(Dr. J. H. L. Cumpston and Professor H. R. Dew were later appointed to this committee, the creation of which was announced by the Minister for Air on December 4.)

Reference was made to one not unimportant sidelight of the war—the care of evacuee children brought to Australia from the war zones. Dr. Newman Morris referred to the booklet on "The Care of the Child" which is being compiled by the Victorian Division of the Australian Red Cross in association with other interested organizations. This

booklet is intended for the guidance of women and girls who may be entrusted with the care of evacuee children. Dr. Morris said that this was a definite attempt to meet the problems of these children, many of whom must show some reaction from the experiences through which they have passed.

Venereal Disease.

At the ninth session of the council, in May, 1940, special reference was made to the problem of venereal disease, brought into sharper focus under war conditions. It was then recommended that this subject should be a major one for discussion at this session and that it might be possible to convene a preliminary session of specialist medical officers from the several States to exchange opinion and experience of their work in the control and treatment of venereal disease. It was not found practicable to convene such a conference at this session of the council, but the session was attended by Dr. J. Cooper Booth, Director of the Division of Social Hygiene of the New South Wales Department of Public Health.

Dr. Cooper Booth gave to the session his experience of the practical working of venereal disease legislation in New South Wales. He felt that their methods of getting defaulters to return to treatment were becoming increasingly effective, but one loophole in the legislation in New South Wales, which is covered in other States, is the lack of authority to order persons suspected of infection to submit to examination and treatment, with detention if necessary. The police are doing good work in rounding up women on the streets, but the amateur still remained the major source of infection, especially of gonorrhœa. He quoted figures of sources of infection obtained from a very large number of patients attending clinics in Sydney. The percentages of infection for married and single men were recorded as follows:

Gonorrhœa:			
Married 22·7%, infected from		Amateur	54·8%
		Prostitute	9·5%
		Wives	35·7%
Single 77·3%, infected from		Amateur	83·6%
		Prostitute	16·4%
Syphilis:			
Married 22·4%, infected from		Amateur	38·7%
		Prostitute	26·7%
		Wives	34·6%
Single 77·6%, infected from		Amateur	67·8%
		Prostitute	32·2%

A feature of venereal disease incidence in New South Wales within recent years has been the apparent increase of cases of primary syphilis, an increase which dates from 1938, the year of the sesquicentenary celebrations. Before that year the State had shared with other States in an almost complete disappearance of primary syphilis. Over the past four years, to October 31, 1940, the percentage of primary cases to all cases of syphilis under treatment had been as follows:

1937	8·8%
1938	17·5%
1939	34·2%
1940	29·5%

With regard to gonorrhœa, the graph of infections among males had shown a marked drop during the year. He thought that the new forms of chemotherapy might have had the effect of patients seeking treatment from chemists and quacks. One danger in this arises from the fact that some 1·8% of all cases are double infections of syphilis and gonorrhœa, and if the drop in notifications of gonorrhœa means secret treatment of that disease, it means also that cases of syphilis are being missed and untreated.

For the more effective control of venereal diseases he advocated four measures: (i) premarital certificates of health; (ii) blood tests of all pregnant women as a routine; (iii) close cooperation between the medical services of Navy, Army and Air Force and the civil health authorities; (iv) the regular circulation of information concerning new developments in treatment and the exchange of experience between those concerned in all States.

In a discussion following this paper there was general agreement that legislation in Australia had achieved success in that advance had been made by the provision of adequate clinic facilities and proper specialist treatment; the public had been educated to the dangers of disease and the necessity for treatment; whilst power was held to deal with the defaulter who refused continued treatment after tactful approach by correspondence and visits from carefully selected trained nurses or social workers. The desirability of premarital examination was recognized, but it was felt that any compulsory system was impracticable until public education, especially of women, had created acceptance of its value. The report of a select committee in Tasmania on this subject is awaited with interest. Other States (excepting New South Wales) have not apparently experienced any increase in cases of primary syphilis. The eleven Commonwealth Health Laboratories throughout Australia carry out Kline tests for syphilis free of charge and no increase of new infections has been reported. The routine blood examination of expectant mothers was regarded as a very important measure which should eliminate congenital syphilis in the community. Relevant figures were quoted from Victoria, where in 1920 Fowler reported 10% positive results in the Women's Hospital; in 1932-1936, in over 16,000 tests at the Queen Victoria Hospital, only 1·02% of results were positive; in 1937-1940 this figure had been reduced to 0·06%.

On the question of the treatment of gonorrhœa it was suggested that with the new therapy more patients were being treated by the general practitioner; there should be a wider recognition that a danger existed in the cessation of treatment when visible signs had cleared up and the symptomless but still infective patient was discharged from treatment.

The council throughout this discussion bore in mind the social problems associated with war conditions; whilst appreciating what has been done by education, prophylaxis and medical attention in the services, it was felt that there should be closer cooperation between the services and civil authorities in attacking a problem which now and after the war is one which affects the whole community. To ensure that cooperation, the council resolved that:

> In view of the grave importance of venereal disease in relation to cross-infections between persons in civil life and persons in military service, the council considers it is very necessary that the civil health authorities should be aware of the incidence and methods of control of these diseases in the Navy, Army and Air Force, and requests the chairman to obtain information on these points from the medical authorities of the three services and circulate this information amongst the States.

Cerebro-Spinal Meningitis.

A rising incidence of cerebro-spinal meningitis during the late winter of 1940 recalled the experience of 1915, when, in circumstances similar to those which exist today, this disease flared into epidemic prevalence in the civil community and in military camps. In 1916 every State was affected, 1,456 cases were notified and there were 405 deaths from the disease. The experience of the epidemic years of 1915-1918, the reported prevalences of this year, and measures taken to combat epidemic spread were reported to this session of the council by Lieutenant-Colonel M. J. Holmes who, in 1915-1916, investigated and reported upon the outbreaks of those years and who is now Director of Hygiene at Army Headquarters.

Lieutenant-Colonel Holmes referred to a widely held view which, he said, required modification in the light of experience, that "overcrowded military establishments in time of war must be regarded as the main source of all widespread epidemics". (this was quoted in the very adequate review of cerebro-spinal meningitis which appeared in THE MEDICAL JOURNAL OF AUSTRALIA, July 20, 1940, page 51). In 1915, when in Victoria the first camp epidemics occurred in August at Seymour and Flemington, there had been already at least 50 cases of cerebro-spinal meningitis reported over several months from the metropolitan area and from districts as widely separated as Ballarat, Bendigo, Healesville, Mooroopna and Drouin. August saw camps overcrowded with raw recruits, training hard in wintry weather; when upper respiratory tract infections were prevalent both in and out of camp. There had been sporadic cases in camp during previous weeks, and in the Seymour and Flemington camps, with the influx of new recruits, there were 80 cases within three weeks of the commencement of the epidemic. The incidence then fell quickly during September. This was typical of the camp epidemics, but in the civil community the disease continued at a fairly high level to fall gradually through the following summer. In 1916 a rising incidence again appeared in the civil community prior to the reappearance of cases in military camps. The camp epidemics were again short and sharp. In the civil community, however, incidence continued to rise after the camp epidemics had subsided. This experience was common to all States.

In the military camps epidemic prevalence was associated with three special factors: (i) excessive overcrowding; (ii) influx of a large number of unsalted recruits into a camp in which infection is present; and (iii) a high rate of upper respiratory tract infection with persistent coughing. All these factors were associated in marked degree with the camp epidemics of 1915-1916.

In July, 1940, an increase in civil notifications of cerebro-spinal meningitis occurred in New South Wales, to be

followed by rising figures in Victoria and Western Australia. The increase in civil incidence was accompanied by sporadic cases in military camps in New South Wales and Western Australia, but not at first in Victoria. By the end of October 150 cases had been reported in the Commonwealth (New South Wales 35, Victoria 49, Queensland 6, South Australia nil, Western Australia 55, Tasmania 5), 27 in the services and 123 amongst civilians. Army cases numbered 24, distributed in 16 different camps. In half of these cases the patients had been six weeks or less in camp.

Control measures had been prepared in anticipation of the appearance of the disease in military camps. Briefly the action taken on the occurrence of a case or suspicious case in a camp was as follows:

1. Full details were notified to the Director-General of Medical Services, and advice was sent to State Health Department and local authorities, including particulars of civilian contacts.

2. The patient was isolated immediately in the camp, and treatment with sulphapyridine in full dosage was commenced as soon as swabs had been taken and lumbar puncture performed for diagnostic purposes, but without awaiting the confirmation of diagnosis.

3. The patient was removed to isolation hospital as soon as practicable.

4. Immediate steps were taken to confirm the diagnosis by bacteriological methods. For this purpose before sulphapyridine was administered naso-pharyngeal swabs were taken, lumbar puncture was performed and blood culture might be attempted.

5. The close contacts of the case were put under observation but were not isolated. At the discretion of the deputy director of medical services or senior medical officer naso-pharyngeal swabs might be taken and examined if facilities for the efficient performance of this work were available. Close contacts were those who occupied beds immediately adjacent to the patient, and any others judged by the medical officer to have had close or prolonged contact.

6. If any close contact under observation developed catarrhal or other signs suspicious of a commencing meningococcal infection he was isolated and treatment with sulphapyridine was commenced without awaiting the results of naso-pharyngeal swabbing.

7. Careful watch was maintained in the unit and in the camp generally to detect clinically suspicious cases at the earliest possible moment. Men suffering from catarrh were specially watched.

8. Army instructions for the relief of over-crowding in camps had already been enforced. Additional accommodation in camps was being provided as rapidly as possible, and recruiting activity had been conditioned by the accommodation available. In any camp where cerebro-spinal meningitis occurred everything possible was done to overcome any overcrowding which might exist. Strict attention was paid to the maintenance of ventilation in the sleeping and other quarters, and to prevent undue crowding together in recreation huts *et cetera*. The men received instruction in personal hygiene in relation to droplet infection.

9. Action was taken in relation to cleanliness of tents and huts. In the tents the floor boards were moved periodically into the sunlight and tent sides were turned up to give the sunshine direct access to the space beneath the tents. Huts were thrown open and washed out with disinfectant solution.

10. Leave from the camp was not interfered with except that close contacts under observation were not given leave until the period of observation had expired. Visitors were not debarred from the camp, but they met the troops only in the open air.

If cases of cerebro-spinal meningitis continued to occur in the camp, thus providing evidence of persistent infection, additional precautions were taken to stop as far as practicable the entry of recruits to the camp, leave and visitors to the camp were more strictly controlled, and no children were permitted to enter the camp.

With regard to treatment of patients, full instructions had been issued to military medical officers. Sulphapyridine was employed in full dosage and in fulminant cases initial dosage was given by the intramuscular and intravenous routes. Dosage was watched by the estimation of the concentration of sulphapyridine in the blood and cerebro-spinal fluid. A leucocyte count was taken on the third day and again later. Three of the 27 service patients had died, one infection was fulminant and the patient died within six hours of the commencement of treatment. Lieutenant-Colonel Holmes's report will be published in full in a subsequent issue.

In a discussion following Lieutenant-Colonel Holmes's report, the importance of cooperation of military and civil authorities was stressed.

Dr. E. Atkinson reported that in Western Australia, amongst patients treated at Government hospitals, there had been three deaths (11% of admissions) compared with a 50% mortality in the epidemic years of the last war.

There was general agreement that swabbing of contacts was now useful only in exceptional circumstances, possibly in institutions or on certain occasions to be judged on the individual merits of the case. Comment was made on one administrative difficulty which often now arose: the public was prone to demand mass swabbing as a routine measure of epidemic control, attributing magic properties to the swab itself.

In reply to a question, Lieutenant-Colonel Holmes considered that administration of small doses of sulphapyridine to close contacts in civilian households was unnecessary; it should be sufficient to watch contacts and to commence dosage on the first suspicion of symptoms in any contact.

Physical Fitness.

The Commonwealth Council for National Fitness[1] met at Canberra concurrently with this session of the National Health and Medical Research Council. On November 6 a joint session of the two councils was held. Resolutions of the Council for National Fitness were presented, including recommendations for a central Commonwealth organization, with a full-time Director, to provide a central focus for cooperative action in all States. The aims of the movement and the programme contemplated by the National Fitness Council were explained by Mr. R. E. Halliday, of Western Australia, Mr. W. Martin, of South Australia, and Mrs. I. Weber, of Victoria.

Mr. R. E. Halliday called attention to the fact that there were no Australian objective standards of body measurements, of nutrition and so on. Many complicated systems were advocated, but there was an obvious need for much research and a coordinated plan. He suggested that the movement in Australia must supply such a plan with a Federal body to stimulate the coordinate activities. In Western Australia they were trying to develop an Australian system of physical training to deal especially with the age groups between fourteen and eighteen. In the recent course of certificates at the Western Australian University, there were over 90 candidates and the Western Australian Branch of the British Medical Association had cooperated in the giving of lectures. He stressed the view that the overseas systems, such as the Swedish, Danish and so on, were not applicable *in toto* to Australian conditions and in Western Australia they were trying to develop something which really was applicable.

Mr. W. Martin stated the objectives of the physical fitness movement—to educate the public, to coordinate existing organizations, to provide leaders for education and training and to inquire into the causes and remedies of unfitness. He felt that there should be a common purpose in all States to obtain real results. He described the South Australian machinery and organization in which medical support was in evidence and there was a vigorous committee with an executive and nine subcommittees. They now had a university course, they had established a South Australian Association of Boys' Clubs, a national fitness week, a summer school and camp, and had stimulated activities of the local authorities to assist physical fitness. He felt that much more was to be done and that this would be achieved with a central Commonwealth direction and increased funds. They themselves would be able to provide all the necessary local services.

Mrs. I. Webber called attention to the fact that Victoria had initiated the first university course in physical fitness in 1935 when Dr. Duras, under Carnegie Corporation funds, established the course. Diplomates have already passed and gone to both boys' and girls' schools. The Victorian council was launched at a difficult period at the beginning of the war, and despite some criticism and difficulties, they had been able to pioneer quietly and in an unspectacular way a really effective organization. Here again medical support had been considerable. She felt that this physical fitness movement was national service and, though it was right that the Department of Health should administer the scheme, there should be collaboration with the new Ministry of Labour and National Service. She called attention to work which was being done in Victoria in regard to first aid, sick nursing and child management which was a matter that had arisen in connexion with the arrival of child evacuees from England. This brought the question back again to the

[1] The Minister for Health (the Honourable Sir Frederick Stewart, M.H.R.), the Honourable H. E. Holt, M.H.R., Dr. J. H. L. Cumpston, C.M.G., Mr. A. R. Symons (New South Wales), Mrs. I. Weber, M.L.A. (Victoria), Sir Raphael Cilento (Queensland), Mr. W. Martin (South Australia), Mr. R. E. Halliday (Western Australia), Mr. J. H. Geappen (Tasmania).

mother and a matter which they felt was important was that the mother should not be discharged from hospital too soon after confinement and that provision should be made for home help or a holiday for every mother for at least fourteen days a year. Another matter which she considered of importance was the question of the standard and registration of diplomates from the university courses.

Dr. J. H. L. Cumpston recalled the resolutions of the fourth session of the National Health and Medical Research Council (May, 1938) and he pointed out that the physical fitness movement really originated from this resolution of council.

Dr. E. S. Morris responded on behalf of the council, expressing gratification for the development of the movement and that difficulties of organization and of personalities had been straightened out. He felt that the pace of public education was increasing and that public opinion would eventually compel Government assistance. One difficulty he foresaw in the training for certificates and diplomas was that a competitive spirit might develop between the different States. He felt that there should be a common level and standard. He agreed with the suggestion of central coordination and that it would be a good thing to remove differing standards and ideals if they could do so without finding a deadening uniformity.

Nutrition.

The council, in developing its research system, has received great assistance from the committees which have been coopted to assist the advancement and the critical supervision of investigations in special fields. Such committees have been appointed in obstetrics, tuberculosis, tropical physiology and hygiene, dental research and nutrition. On the occasion of this session, arrangements were made for a meeting of the Nutrition Committee[1] at Canberra and for a joint session with the full council to discuss problems of particular importance at the present time.

One question which has aroused very wide interest is that of fortifying the white loaf of bread with a supplement of vitamin *B* (aneurin) and a calcium salt. An announcement that this measure was being adopted in England was made in the House of Commons on July 18, 1940, by the Parliamentary Secretary to the Ministry of Food. It was explained that this move had been made because it was recognized that the lesser nutritive value of white bread, compared with wholemeal, resulted from the relatively low vitamin *B* content of white bread, whilst dietary surveys had established that the nation as a whole was not receiving sufficient vitamin *B*. Calcium was added because there was some evidence that calcium was deficient in many diets and bread was an obviously satisfactory article of food to which it could be added.

This decision of the British Government formed the basis of an extensive discussion by the Nutrition Committee which gave earnest consideration to the possible need of recommending a similar move in Australia.

The committee was of the opinion that no evidence existed at the present time to indicate that the Australian community, or any part of it, was suffering from even partial vitamin *B* deficiency. Some experiments, however, conducted in the United States of America, had indicated that partial vitamin *B* deficiency could exist in the community virtually unrecognized, and that it was possible that certain minor departures from normal health might be attributed to vitamin *B* deficiency. Because of these facts, the committee had decided to recommend the adoption of a number of special investigations in an endeavour to determine this question in Australia.

The British authorities had stated that the average vitamin *B* content of white flour milled in England was 2·7 international units per gramme. A series of preliminary determinations made at the Australian Institute of Anatomy, Canberra, on a number of specimens of white flour drawn from all over Australia had shown that the vitamin *B* content of these samples ranged from 120% to 300% above that given for flour milled in England. Preliminary determinations of the vitamin *B* content of a number of varieties of wheat grown in Australia had confirmed the suggestion made overseas that Australian wheats were the richest in the world in vitamin *B*.

The Federal Executive of the Flour Millers' Association had shown a practical interest in these experiments by offering £600 to finance continuation of the work. The Nutrition Committee recommended that this grant be gratefully accepted and that the National Health and Medical Research Council might supplement this sum with a further £400 to enable a complete survey to be made of the vitamin *B* content of Australian wheat and flour. Facilities existed for this work at the Australian Institute of Anatomy, Canberra, and the Department of Biochemistry in the University of Melbourne.

The present attitude of the Nutrition Committee to the whole problem was adequately summarized at the end of a relevant resolution:

> The Committee is of the opinion that the addition of synthetic vitamin *B* alone to white flour involves a wrong principle. It is well known that there are many substances, where mixtures occur in natural products, which have a more beneficial effect than the administration of the isolated single substances. An example is seen in the treatment of pellagra where it has been found that whereas the primary deficiency is nicotinic acid, the best results are obtained by the administration of additional members of the vitamin *B* complex. There is no evidence that vitamin *B* produces its complete nutritional effect by its own physiological action or that it is any more deficient in the diet of the general Australian community than any other members of the *B* complex and other substances necessary for normal nutrition.

The council, following consultation with the Nutrition Committee at the joint session, adopted a resolution that:

> The council resolves that the report of the Nutrition Committee be adopted, the resolutions be endorsed, and the grants be recommended.

In the field of child nutrition, a special investigation on calcium and phosphorus metabolism of infants and young children is being continued, under a research grant, at the Renwick Hospital in Sydney. It should also be noted that through reports of its own Nutrition Committee and through reports brought by members from all States from their own departments and from semi-official and voluntary agencies, the council maintains a close watch on work done and problems encountered throughout the Commonwealth in this important field.

Leprosy.

In Queensland, survey work under a grant from the council lapsed during 1939 with the illness and the later enlistment of the medical officer. No other suitable medical officer was available. Consultations on the possibilities of continuing this work and on the whole problem of control of leprosy, in Europeans and aboriginals, were arranged between Sir Raphael Cilento and Dr. C. E. Cook, of the Sydney School of Public Health and Tropical Medicine. Administrative difficulties, especially of staff, are inevitable in this work, but definite advances have been made in the establishment at Fantome Island for aboriginal patients and suspects, and the whole problem remains under constant review. In Western Australia the two years' work of Dr. L. A. Musso, under a grant from the council, has been carried out effectively under difficult conditions. Dr. Musso has carried out arduous patrols into the north-west and the Kimberleys with considerable success. As a result there are now over 200 patients under treatment in the leprosarium at Derby. (At December 31, 1939, there were 394 patients in leper hospitals in the Commonwealth, including 47 Europeans.)

Chronic Rheumatism.

Dr. J. Newman Morris stated that he had been asked by the Federal Council of the British Medical Association in Australia to suggest that the National Health and Medical Research Council might again consider research into the problem of chronic rheumatism. No scheme for special investigation in this field was before the council and it was considered that since the war had dislocated so many research resources, no immediate action was practicable. It was agreed, however, that the matter would be kept under consideration.

Health Education.

At each session of the council members from each State exchange experience of the results of new and old methods of health propaganda and popular education. Appreciative reference has been made to the weekly broadcasts of the "B.M.A. Spokesman" arranged by the special committee of the New South Wales Branch of the British Medical Association. At the eighth session of the council (May, 1940) Dr. E. S. Morris described the records of short health talks prepared for broadcasting by his department in New South Wales. He suggested that it might be possible to develop

[1] Professor Sir Stanton Hicks, Professor D. H. K. Lee, Dr. Ivan Maxwell, Professor H. Priestley, Mr. E. Underhill, Professor W. J. Young, and Dr. F. W. Clements (convener).

an Australian library of such records which he had found acceptable to the broadcasting stations. During this recent session he arranged for two such talks to be broadcast, on nutrition and on personal health and periodical medical examination. A novel feature was therefore introduced into the session of the council when members listened to short, popular and very apposite talks on subjects on their own agenda.

Housing.

Whilst moving a vote of thanks to the chairman, Dr. J. F. Gaha said that he wished to raise one question which did not appear on the agenda. He said that he realized that the problems of housing were controversial, but he would submit by correspondence a proposal that the council should make a forward move with regard to the whole question of the housing of the people.

Place and Time of Next Meeting.

The council agreed to leave in the hands of the chairman the question of the place and time of next meeting of the council. (It is now customary to hold sessions twice a year, in May and November.)

Naval, Military and Air Force.

WIRELESS TRANSMITTING APPARATUS (POSSESSION) ORDER.

THE following explanatory statement on a wireless transmitting apparatus order has been received for publication from Surgeon-Captain W. J. Carr, Director of Naval Medical Services, who forwarded it at the request of the Department of the Navy.

In order to avoid the possibility of diathermy and other high-frequency electrical apparatus causing interference to defence and other essential radio services, and to minimize the possibility of such apparatus being put to improper use, an order has been made under the National Security (General) Regulations, which will come into effect from April 1, 1941.

This order requires that no person, association, company, hospital, clinic or institution shall possess or operate the following types of apparatus without a licence, if such apparatus develops power exceeding 10 watts at frequency exceeding 10,000 cycles per second:

(*a*) Diathermy or other electro-medical apparatus in which valves or spark coils are used, not including normal modern types of violet ray, ultra-violet ray, infra-red ray, or X-ray apparatus, or medical shocking coils.
(*b*) High-frequency furnaces.
(*c*) Eddy current heating apparatus.
(*d*) High-frequency testing oscillators.

Before a licence to operate any of the above equipment is issued, the apparatus, or the room or premises in which the apparatus is installed, must be screened or otherwise treated so that interference will not be caused to authorized radio services.

Those who may suffer inconvenience from this order will appreciate the necessity for such steps in time of war. In the United Kingdom the equivalent regulation forbids absolutely the possession of diathermy apparatus by any private individual and even by private hospitals and clinics, but the Australian authorities consider that the situation does not warrant such sweeping action in the Commonwealth.

Persons in possession of apparatus of the types listed above are required to make application to the Senior Radio Inspector of the Postmaster-General's Department of the capital city in the State in which the applicant resides, or, if the applicant resides in a Territory, to an officer in that Territory thereto authorized in writing by the Postmaster-General. The application requires the following particulars:

1. Name and address and occupation of applicant.
2. Date and place of birth.
3. Names and nationalities of persons who will be permitted to operate the apparatus.
4. Address at which the apparatus is or will be lodged or installed.
5. Description of the apparatus, including power, manufacturer's name, type, and other particulars.
6. Purpose for which it is desired to install the apparatus.
7. Description of screening, shielding, or other treatment provided, or to be provided, so as to render the apparatus incapable of radiation which may cause interference with authorized radio services.

MEDICAL OFFICERS REQUIRED FOR CAMPS IN NEW SOUTH WALES.

MEDICAL OFFICERS are urgently required for full-time duty (home service) with the Australian Army Medical Corps in the Eastern Command Area. The increased period of service in camps is inflicting a certain amount of hardship on members of militia units. This is obviated to some extent by a system of rostering whereby men go into camp for a period of at least one month, instead of for the full period of 90 days, but even in these circumstances many units are shorthanded. It is thought that a considerable number of men might undertake this duty by mutual arrangement for conduct of their practices. Men who feel that they are not physically capable of carrying out drill in militia camps can be usefully employed in clinical work in camp hospitals. In some country towns there is urgent need of men with surgical experience who would undertake the performance of surgical operations in country camps. Those willing to offer their services should apply to Colonel A. M. McIntosh, D.D.M.S., Eastern Command, Victoria Barracks, Sydney.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 26, of February 13, 1941.

AUSTRALIAN MILITARY FORCES.

SOUTHERN COMMAND.

Third Military District.

Australian Army Medical Corps.

To be Captain (provisionally).—Harold Bickford Hattam, 25th January, 1941.

Major C. E. Watson, M.C., is appointed to command a Field Ambulance and to be Lieutenant-Colonel (temporarily), 28th November, 1940.

Major (Temporary Lieutenant-Colonel) C. E. Watson, M.C., relinquishes command of a Field Ambulance and the temporary rank of Lieutenant-Colonel, 15th January, 1941.

Lieutenant-Colonel I. Blaubaum is appointed to command a General Hospital, 1st December, 1940.

Captain A. R. Buchanan is appointed from the Reserve of Officers (A.A.M.C.), 6th October, 1940, and to be Major (temporarily), 9th December, 1940 (in lieu of the notification respecting this officer which appeared in Executive Minute No. 232/1940, promulgated in *Commonwealth Gazette* No. 258 of 1940).

WESTERN COMMAND.

Fifth Military District.

Australian Army Medical Corps.

Honorary Captain G. A. Kelsall is appointed from the Reserve of Officers (A.A.M.C.) and to be Captain (provisionally) 13th January, 1941.

Captain S. Finkelstein is transferred to the Reserve of Officers (A.A.M.C.), 11th January, 1941.

Correspondence.

MEDICAL CURE OF PERINEPHRIC ABSCESS.

SIR: I have read Dr. H. Ross Macourt's report entitled "Medical Cure of Perinephric Abscess" (THE MEDICAL JOURNAL OF AUSTRALIA, February 15, 1941, page 206) with great interest.

However, I cannot agree with the clinical diagnosis of a perinephric abscess in his patient. The history is typical of a perirenal hæmatoma following an accident. These patients have a raised temperature and a high pulse rate, and even a rigor in the stage of abortion of the blood clot. They respond well to conservative treatment, whereas a perinephric abscess always requires surgical intervention and, when properly incised, heals up rapidly in an uncomplicated case.

Yours, etc.,

T. ROSE, F.R.C.S.

Commonwealth Bank Chambers,
Newcomen Street,
Newcastle, New South Wales.
February 14, 1941.

THE MEDICAL EYE SERVICE OF NEW SOUTH WALES.

SIR: You will be interested to learn that on Monday, March 3, 1941, the Medical Eye Service of New South Wales will open in new and commodious premises, which have been built for the purpose, at 27-29 Commonwealth Street, Sydney.

The building will be open for inspection by the members of the British Medical Association on Saturday, March 8, 1941, from 1 p.m. to 4.30 p.m., and all members are cordially invited.

Yours, etc.,

D. A. WILLIAMS,
Honorary Secretary.

Sydney,
February 21, 1941.

Obituary.

ARCHIBALD JAMES CUNNINGHAM.

WE regret to announce the death on active service of Lieutenant-Colonel Archibald James Cunningham, of the Australian Army Medical Corps.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Bourke, Herbert Merwin, M.B., B.S., 1922 (Univ. Adelaide), 604 Railway Parade, Hurstville.

Douglas, Raymond Lindsay, M.B., B.S., 1940 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.

The undermentioned has applied for election as a member of the Victorian Branch of the British Medical Association:

Reeves, Thomas Conrad, M.R.C.S. (Eng.), L.R.C.P. (Lond.), 1911, 153 Foster Street, Dandenong.

The undermentioned has applied for election as a member of the Tasmanian Branch of the British Medical Association:

Lewis, Reginald A., M.B., B.S., 1936 (Univ. Melbourne), Launceston General Hospital, Launceston.

The undermentioned has applied for election as a member of the South Australian Branch of the British Medical Association:

Semler, Clifford Gerhardt, M.B., B.S., 1940 (Univ. Adelaide), Royal Adelaide Hospital, Adelaide.

The undermentioned has been elected a member of the South Australian Branch of the British Medical Association:

Pellew, Richard Alfred Amyas, M.B., B.S., 1934 (Univ. Adelaide), Captain, 2/3 Machine Gun Battalion, Australian Imperial Force, Abroad.

Medical Appointments.

Dr. John Michael Tighe has been appointed to act as Medical Inspector of Seamen at Onslow, Western Australia, pursuant to the provisions of the *Navigation Act*, 1912-1935.

* * *

Dr. Campbell Amiet Duncan, Commonwealth Department of Health, has been appointed Medical Officer, Third Division, in Tasmania.

Books Received.

"Hutchison's Food and the Principles of Dietetics", revised by V. H. Mottram, M.A., and G. Graham, M.D., F.R.C.P.; Ninth Edition; 1940. London: Edward Arnold and Company. Demy 8vo, pp. 675, with diagrams. Price: 21s. net.

"The Art of Surgery: A Text-Book for Students and Practitioners", by H. S. Souttar, D.M., M.Ch., F.R.C.S.; Fourth Edition, in two volumes; 1940. London: William Heinemann (Medical Books) Limited. Large crown 8vo, pp. 779, with illustrations. Price: 25s. net.

Diary for the Month.

MAR. 2-3.—Federal Council of the B.M.A. in Australia: Meeting in Melbourne.
MAR. 4.—Queensland Branch, B.M.A.: Post-Graduate Committee.
MAR. 4.—New South Wales Branch, B.M.A.: Organization and Science Committee.
MAR. 5.—Western Australian Branch, B.M.A.: Council.
MAR. 5.—Victorian Branch, B.M.A.: Branch.
MAR. 6.—South Australian Branch, B.M.A.: Council.
MAR. 7.—Queensland Branch, B.M.A.: Branch.
MAR. 7.—Victorian Branch, B.M.A.: Legislation Subcommittee.
MAR. 11.—Queensland Branch, B.M.A.: Mater Misericordiæ Hospital Clinical Society.
MAR. 11.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
MAR. 11.—New South Wales Branch, B.M.A.: Ethics Committee.
MAR. 11.—Tasmanian Branch, B.M.A.: Branch.
MAR. 13.—Victorian Branch, B.M.A.: Ethics Subcommittee.
MAR. 14.—Queensland Branch, B.M.A.: Council.
MAR. 17.—Victorian Branch, B.M.A.: Hospital Subcommittee.
MAR. 18.—Queensland Branch, B.M.A.: Ear, Nose and Throat Section.
MAR. 18.—New South Wales Branch, B.M.A.: Medical Politics Committee.
MAR. 18.—Victorian Branch, B.M.A.: Organization Subcommittee.
MAR. 18.—Victorian Branch, B.M.A.: Finance, House and Library Subcommittee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia: all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.

Editorial Notices.

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